REMARKS:

Claims 1-5, 8-10, 12-16, 24-46, and 53-55 were pending in the instant application. Claims 1-5 were withdrawn from consideration. Claims 8-10, 12-16, 24-46, and 53-55 were under examination.

Claims 8 has been amended to indicate that a chemically modified erythropoietin may be combined with a prophylactically or therapeutically effective amount of either an anti-inflammatory agent or immunomodulatory agent. Support for this amendment can be found in the specification as originally filed at paragraphs [27] and [30]. Claim 8 has also been amended to recite the particular residues and positions within erythropoietin that may be chemically modified. Support for these residues and positions can be found in the application as originally filed at paragraph: [91]. The amino acid sequence of erythropoietin was well-established in the art. See, *e.g.*, paragraph [05]. In particular, U.S. Patent 4,703,008 (cited in the present application at paragraph [05], line 6; attached as Exhibit A) discloses the amino acid sequence of erythropoietin (see Figure 6 of U.S. Patent 4,703,008). Claim 8 has further been amended to incorporate particular chemical modifications. Support for the addition of these particular chemical modifications to the claim can be found in the specification as originally filed at paragraphs [97] to [108].

Claim 9 has been amended to delete the references to corticosteroids and glucocorticoids.

New claims 56 to 59 have been added. Support for the new claims can be found in the specification as originally filed, *e.g.*, at paragraphs [139] through [142].

No new matter has been introduced. Claims 1-5, 8-10, 12-16, 24-46, and 53-59 will be pending upon entry of the present amendment.

I. OTHER REFERENCES

Applicants wish to draw the Examiners attention to the following co-pending applications: U.S. Patent Application Serial Nos. 10/185,841, 10/188,905, 10/351,640, and 10/573,905. In particular, Applicants wish to draw the Examiner's attention to the following office actions that issued in these applications:

Copies of Office actions for 10/185,841 dated January 9, 2009; May 23, 2008; June 27, 2007; October 5, 2006; January 18, 2006; and April 28, 2005 are enclosed. Copies of

office actions for 10/188,905 dated October 15, 2008; January 8, 2008; December 7, 2006; and March 21, 2006 are enclosed. Copies of office actions for 10/351,640 dated September 19, 2008; March 19, 2008; June 5, 2007; August 28, 2006; and December 13, 2005 are enclosed. A copy of an office action for 10/573,905 dated November 24, 2008 is enclosed.

II. SUMMARY OF THE SUBSTANCE OF THE INTERVIEWS

Applicants thank Examiner Cherie Michelle Woodward for the courtesy extended during the interview conducted on February 4, 2009 at the United States Patent and Trademark Office ("the February 4th Interview'). Also present at the Interview were Drs. Anthony Cerami and Michael Brines, two of the inventors of the instant application, Frederick J. Hamble, Esq. of Warren Pharmaceuticals, Inc., Mary Catherine DiNunzio, Esq. of H. Lundbeck A/S and applicants' representative Eileen E. Falvey of Jones Day.

During the February 4th Interview, the rejections under 35 U.S.C. § 112, first paragraph, made in the Office Action dated September 24, 2008 (the "Office Action") were discussed. The scope of claim 8 was discussed and Applicants directed the Examiner's attention to paragraph 91 of the application where it teaches that chemical modifications within the four EPO receptor binding regions of EPO and the surrounding regions result in chemically modified EPOs having reduced erythropoietic activity. The Examiner suggested adding in the specific residues to claim 8. Additionally, the rejections under 35 U.S.C. § 103(a), particularly the Escary and Satake references, were discussed.

Further Applicants thank Examiner Cherie Michelle Woodward for the telephonic interview conducted on February 24, 2009 with Applicants' representative Eileen E. Falvey of Jones Day ("the February 24th Interview"). During the Interview, Applicant's draft proposal for claims 8 and 54 was discussed and the Examiner provided comments on the claims.

This Amendment, and the remarks herein, reflect the discussion during the February 4th and 24th Interviews.

III. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, ENABLEMENT, SHOULD BE WITHDRAWN

Claims 8-10, 13-16, 43-46 and 54-55 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner maintains

that these claims read on any generic tissue protective cytokine. Without agreeing to the Examiner's rejection and solely to expedite the prosecution of this application, Applicants have amended claim 8 to: (1) recite the particular positions for each of the residues that may be modified; and (2) recite particular types of chemical modifications into the claims. Applicants assert that the specification is enabling for the claimed invention and that the indicated claims should be allowed, for the reasons stated below.

In light of the disclosure of (1) particular amino acid residues located within the EPO-EPOR binding region and surrounding areas (present specification, *e.g.*, at paragraph [91]), (2) particular chemical modifications disclosed within the application and known in the art (present specification, *e.g.*, at paragraphs [97] to [108]), and (3) functional assays to determine that the modifications received the desired changes on the molecules activity, *i.e.* reduction of *in vivo* erythropoietic activity without a loss of tissue protective activity (present specification, *e.g.*, at paragraphs [132] and [133], one of ordinary skill in the art would be capable of practicing the claimed invention without undue experimentation.

Commensurate with this disclosure, the claims specify chemically modified EPOs having the structural and the functional properties set out in the specification – *i.e.*, a chemical modification at one or more of the specifically recited amino acids residues, and tissue protective but reduced erythropoietic activity.

The previously submitted Brines declarations (Brines I and Brines II, see Applicants' responses of June 27, 2008) show that the generation of chemically modified EPOs and the assays for testing the biological activities of these modified forms of EPO would be routine in view of the guidance in the specification and the knowledge in the art. See, Brines I, at paragraphs 6 to 23. The Brines declarations further demonstrate the successful application of the teachings of the present patent application. See, Brines I, at paragraphs 25 to 32. In particular, Brines II, paragraphs 6 to 23 demonstrates the successful application of the presently claimed methods in a wide variety of tissues and organs.

Thus the evidence of record demonstrates that the skilled artisan could have prepared the chemically modified forms of EPO described in the specification using the well-established chemical techniques described in the specification; and could have confirmed the tissue protective activity and reduced erythropoietic activity of such chemically modified EPOs, using well known techniques described in the specification, to obtain chemically modified EPOs specified for use in the currently claimed methods of treatment.

In this regard we note that it is not fatal that a certain amount of experimentation is required to practice the claimed invention – experimentation is permitted, provided the experimentation is routine. *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). Moreover, *considerable* amount of experimentation is permitted if it is merely routine or the specification provides a reasonable amount of guidance and direction to perform such experimentation. *In re Jackson*, 217 U.S.P.Q. 804, 807 (PTO Bd. Pt. App. Int. 1982). In line with the legal standard set forth in cases such as *In re Wands* and *In re Jackson*, any experimentation required to practice the presently claimed methods is merely routine in view of the well-established methods for chemical modification of proteins and testing these proteins for the recited activities.

Thus, in view of the guidance in the present specification and the state of the art at the time of filing the application, the skilled artisan could practice the presently claimed invention without undue experimentation.

Dependent claims 9-10, 13-16, 43-46 and 54-55 depend from claim 8 and incorporate the limitations of claim 8 via their dependencies, and are therefore enabled as well. According, Applicants assert that the specification is enabling for the claimed invention and that the indicated claims should be allowed.

IV. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION, SHOULD BE WITHDRAWN

Claim 8 has been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement because the claim allegedly reads on any generic structurally modified EPO variants having a reduced level of in vivo erythropoietic activity in comparison to native erythropoietin. Without agreeing to the Examiner's rejection and solely to expedite the prosecution of this application, Applicants have amended claim 8 to: (1) recite the particular positions for each of the residues that may be modified; and (2) recite particular types of chemical modifications. Amended claim 8 satisfies the written description requirement as discussed below.

As noted above, Applicants have amended to claim 8 to clearly indicate which amino acid residues may be modified and which particular modifications may be used to alter those particular amino acid residues. In light of the disclosure of the specification at paragraph [91], one of ordinary skill in the art would recognize the particular amino acid residues that

may be modified within the EPO-EPOR binding sites to achieve the compounds that retain their tissue protective activity with a reduced in vivo erythropoietic activity in comparison to native erythropoietin. Further, one of ordinary skill in the art would recognize which additional positions surrounding the binding areas could be modified according to the disclosure of paragraph [91] and SEQ ID NO: 5. Additionally, one of ordinary skill in the art would recognize which chemical modifications may be undertaken to achieve the desired functional compound in light of disclosure of the chemical reactions with which to modify erythropoietin at the amino acid residues are detailed in paragraphs [97]-[108] and in Examples 2-3, and functional assays disclosed within [132]-[133] as well as Examples 4-12. Thus, Applicants assert that claim 8 provides adequate written description for structurally modified EPO variants having a reduced level of in vivo erythropoietic activity in comparison to native erythropoietin. Applicants request that the rejection of claim 8 under 35 U.S.C. § 112, first paragraph, be withdrawn.

V. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, INDEFINITNESS, SHOULD BE WITHDRAWN

Claim 13 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because the phrase "is capable of traversing an endothelial cell barrier" is allegedly unclear since the Examiner asserts that "capable of" may indicate that this is an inherent property of the genus. Applicants submit that the language "capable of" indicates a functional claim limitation and that such language is proper. See, *e.g.*, M.P.E.P., 2173.05(g). An exemplary routine assay for testing this functional property of erythropoietin is disclosed at paragraph 276 of the specification. Thus, the skilled artisan could determine without undue experimentation whether a given erythropoietin is capable of traversing an endothelial barrier.

Claim 9 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because the claim allegedly recites both the genus of steroids and the subgenera/species of glucocorticoids and corticosteroids. Without agreeing to the Examiner's rejection and solely to expedite the prosecution of this application, Applicants have amended claim 9 to delete the terms glucocorticoids and corticosteroids.

Claim 8 has been rejected under 35 U.S.C. § 112, second paragraph, because the Examiner alleges that the term "reduced level of in vivo erythropoietic activity" is indefinite

given that the Applicants appear to suggest that the term is interchangeable with "non-erythropoietic."

As noted within the footnote of Applicants' June 27, 2008 response, the applicants used the term "non-erythropoietic" for referring to forms of EPO with reduced in vivo erythropoietic activity. The application within paragraph [91] teaches that the chemical modification to erythropoietin "produces tissue protective cytokines which maintain an adequate level of activities for specific organs and tissues but not for others, such as erythrocytes." Thus, it is disclosed that the reduced in vivo erythropoietic activity occurs over a spectrum.

Accordingly, the indefinitness rejections of claims 8, 9, and 13 have been overcome, and Applicants request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

VI. THE REJECTIONS FOR NONSTATUTORY OBVIOUSNESS-TYPE DOUBLE PATENTING SHOULD BE WITHDRAWN

Claims 8-10, 12-16, 25, 43, 54 and 55 have been rejected on the ground of nonstatutory obviousness type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,531,121. In response, and without agreeing with the double patenting rejection, Applicants request that the double-patenting rejection be held in abeyance until the claims are indicated to be allowable in the present application.

Claims 8, 13-16, 31, 32 and 43 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 35, 37, 38, 50-60 of co-pending Application No. 10/188,905. As this is a provisional rejection, Applicants will not address this rejection at this time and request that the rejection be held in abeyance.

Claims 8, 15, 16, 28-31, 33, 34, 36, 39, 53 and 54 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 14, 16-21, 25, 28, 29, 61, 62, and 63 of co-pending Application No. 10/185,841 in view of Brines et al. (PNAS USA, 2000 Sept 12; 97(19): 10526-10531). As this is a provisional rejection, Applicants will not address this rejection at this time and request that the rejection be held in abeyance.

VI. THE CLAIM REJECTIONS UNDER 35 U.S.C. § 103(A), OBVIOUSNESS, SHOULD BE WITHDRAWN

Claims 8-10, 12-16, 24-46, and 53-55 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over WO 02/085940 ("Escary"); Satake *et al.* 1990, *Biochemica et Biophysica Acta.* 1038:125-129 ("Satake"); and Brines *et al.* PNAS USA, 2000 Sept. 12; 97(19):10526-10531 ("Brines"). Specifically, the Examiner alleges that these references render the claimed methods obvious because Escary teaches the use of a D70N erythropoietin variant in a method of treating an inflammatory disease within a mammal including the use of Satake teaches various chemical modifications.

A. The Legal Standard

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some reason, either in the prior art references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *Takeda v. Alphapharm*, 83 U.S.P.Q.2d 1169 (Fed. Cir. 2007). Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Further, a finding of obviousness requires that "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. §103(a). In its recent decision addressing the issue of obviousness, *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 USPQ2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 USPQ at 467.

The *KSR* Court rejected a rigid application of the "teaching, suggestion, or motivation" test previously applied by the Court of Appeals for the Federal Circuit. *KSR*, 127 S. Ct. at 1739 USPQ2d at 1395. However, the Supreme Court affirmed that it is "important to identify a reason that would have prompted a person of ordinary skill in the

relevant field to combine the elements in the way the claimed new invention does . . . because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *KSR*, 127 S.Ct. at 1741, 82 USPQ2d at 1396. Thus, consistent with the principles enunciated in *KSR*, a *prima facie* case of obviousness can be established by showing a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference *and* to carry out the modification with a reasonable expectation of success, viewed in light of the prior art. Both the suggestion and the reasonable expectation of success must both be found in the prior art and *not* be based on the applicant's disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988).

With regard to the final point, the *KSR* Court citing *Graham*, upheld the principle of *avoiding hindsight bias* and cautioned courts to *guard against reading into the prior art the teachings of the invention in issue*. 127 S.Ct. at 1742, 82 USPQ at 1397:

> A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See *Graham*, 383 U.S., at 36, 86 S.Ct. 684 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into the use of hindsight'" (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (C.A.6 1964))).

Thus, the principles set forth in *Graham* and in *Dow Chemical* -- which are still good law post-*KSR* -- require that *both* the suggestion and the expectation of success must be found in the prior art, and not from knowledge gained from the applicant's disclosure. In a post-*KSR* decision, the Federal Circuit stated:

> Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.

Takeda v. Alphapharm, 83 U.S.P.Q.2d 1169 (Fed. Cir. 2007). Thus, even post-*KSR* the prior art must teach a reason for the modification that would lead to the claimed invention.

B. No Reason To Modify Escary

Escary fails to teach several aspects of the presently claimed invention. First, Escary fails to teach *chemically modified* erythropoietin. Second, Escary fails to teach erythropoietin with reduced erythropoietic function. And third, at the heart of Escary's teachings is the treatment of anemia and not the treatment of an inflammatory disease.

Because Escary is concerned with the treatment of anemia (see, *e.g.*, the paragraph spanning pages 29-30), the skilled artisan would not have had a reason to modify the erythropoietin molecule to be non-erythropoietic; on the contrary, the skilled artisan would have sought to retain the erythropoietic activity of erythropoietin.

In addition, there is nothing in the cited art that would point the skilled artisan to the use of non-erythropoietic erythropoietin molecules for the protection of tissue. In fact, none of the cited references points to the separation of erythropoietic and tissue-protective function of erythropoietin to arrive at the presently claimed methods.

C. No Reason To Modify Satake or Brines

Satake is merely concerned with the effect of certain chemical modifications on the erythropoietic activity of erythropoietin. There is no indication in Satake that these forms of EPO would be suitable for the presently claimed methods. In fact, Satake does not even hint at the possibility that non-erythropoietic forms of EPO may retain any biological activity, let alone anti-inflammatory activity.

Brines demonstrates the neuroprotective activity of recombinant human erythropoietin. Brines does not, however, show that chemically modified, non-erythropoietic forms of EPO can retain anti-inflammatory activity.

Thus, the cited references individually, or in combination, fail to make the presently claimed invention obvious. Accordingly, Applicants request that the obviousness rejection of claims 8-10, 12-16, 24-46, and 53-55 over Escary, Satake, and Brines be withdrawn.

CONCLUSIONS:

Applicants respectfully request that the foregoing remarks and amendments be made of record in the file history of the instant application. Applicants estimate that the remarks and amendments made herein place the pending claims in condition for allowance.

Respectfully submitted,

Date: March 24, 2009

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/185,841	06/26/2002	Michael Brines	10165-015-999	4194

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/185,841	BRINES ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,14,16-21,25,61,62 and 64* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,17,25,61,62 and 64* is/are rejected.

7)☒ Claim(s) *7,14,16 and 18-21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/23/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 23 October 2008 has been entered.

Status of Application, Amendments and/or Claims

The amendment and Applicant's arguments, filed 23 October 2008, have been entered in full.

Claims 2-6, 8-13, 15, 22-24, 26-60 and 63 are canceled. New claim 64 was added. Claims 1 and 62 was amended.

Claims 1, 7, 14, 16-21, 25, 61, 62 and 64 are under examination.

Information Disclosure Statement

The information disclosure statement(s) (IDS) (filed 23 October 2008) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been

placed in the application file and the information referred to therein has been considered as to the merits.

Withdrawn Objections And/Or Rejections

The rejection to claims 28 and 29 under 35 U.S.C. 102(b) as being anticipated by Bany-Mohammed et al., Pediatric Research (1996) Vol. 40, No. 3, pages 381-387, as set forth at pages 4-5 of the previous Office Action (23 May 2008), is *withdrawn* in view of the amendment (23 October 2008).

The rejection to claims 28 and 29 under 35 U.S.C. 102(b) as being anticipated by Okuda et al., Digestion 1996, 57:328-332 (Reference submitted by Applicant in Appendix B, 20 February 2008), as set forth at page 6 of the previous Office Action (23 May 2008), is *withdrawn* in view of the amendment (23 October 2008).

The rejection to claims 28 and 29 under 35 U.S.C. 102(b) as being anticipated by Westenfelder et al. Kidney International Vol. 55:808-820, 1999 (Reference submitted by Applicant in Appendix B, 02/20/08), as set forth at page 7 of the previous Office Action (23 May 2008), is *withdrawn* in view of the amendment (23 October 2008).

The rejection to claims 28 and 29 under 35 U.S.C. 102(b) as being anticipated by Mioni et al., Acta Endocrinologica 127:459-65, 1992 (Reference submitted by Applicant in Appendix B, 02/20/08), as set forth at pages 7-8 of the previous Office Action (23 May 2008), is *withdrawn* in view of the amendment (23 October 2008).

The rejection to claims 28 and 29 under 35 U.S.C. 102(b) as being anticipated by Swaak WO 96/14081(Reference submitted by Applicant in Appendix B, 02/20/08), as

set forth at page 8 of the previous Office Action (23 May 2008), is *withdrawn* in view of the amendment (23 October 2008).

The objection to the amendment (filed 20 February 2008) under 35 U.S.C. 132(a) because it introduces new matter into the disclosure, as set forth at pages 8-9 of the previous Office Action (23 May 2008), is *withdrawn* in view of the amendment (23 October 2008).

The rejection to claims 1, 7, 14, 16-21, 25, 61 and 63 under 35 U.S.C. 112, first paragraph, written description (new matter), as set forth at pages 9-12 of the previous Office Action (23 May 2008), is *withdrawn* in view of the amendment (23 October 2008).

The objection to claim 62, as set forth at page 12 of the previous Office Action (23 May 2008), is *withdrawn* in view of the amendment (23 October 2008).

NEW CLAIM REJECTIONS/OBJECTIONS

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 17, 25, 61, 62 and 64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 27 and 28 of copending Application No. 11/631,458. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims are drawn to a method for protecting, maintaining, enhancing or restoring the function or viability of EPO-responsive mammalian cells, tissues and organs comprising administering to a mammal a therapeutically effect amount of an EPO having at least one of the following modifications: at least one or more modified lysine residues or a chemical modification of the N-terminal amino group of the EPO molecule.

The claims of copending Application No. 11/631,458 are drawn to a method for treating a condition or disease of an excitable tissue comprising administering a non-toxic amount of the pharmaceutical composition of claim 22. The pharmaceutical of claims 21 and 22 is an EPO comprising a modified lysine residues of the erythropoietin molecule.

Because the claims of copending Application No. 11/631,458 are drawn to a method for treating a condition/disease of an excitable tissue by employing the same chemically-modified EPO pharmaceutical composition as the instant application, it would be obvious to modify the method of application '458 to include the biological

activity of enhancing/restoring the function or viability of EPO-responsive cells. If a condition/disease is being treated, the function or viability would be enhanced/restored. Furthermore, it would be expected that the chemically-modified EPO of application '458 would similarly have the biological activity of not causing an increase in hemoglobin concentration or hematocrit, as recited in the instant claims, because the same chemically-modified EPO (i.e. carbamylated lysine residues) is being employed in both applications.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 17, 25, 61, 62 and 64 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 37, 50-52, 54 and 59 of copending Application No. 10/188,905. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims are drawn to a method for protecting, maintaining, enhancing or restoring the function or viability of EPO-responsive mammalian cells, tissues and organs comprising administering to a mammal a therapeutically effect amount of an erythropoietin having at least one of the following modifications: at least one or more modified lysine residues or a chemical modification of the N-terminal amino group of the erythropoietin molecule.

The claims of copending Application No. 10/188,905 are drawn to a method for the protection against tissue injury, prevention of tissue injury, restoration of tissue function or regeneration of tissue and tissue function in a mammal comprising administering to a mammal a tissue protective cytokine comprised of a chemically modified erythropoietin having at least one of the following modifications: at least one or more modified lysine residues or a chemical modification of the N-terminal amino group of the erythropoietin molecule.

It would be obvious to modify the method in copending Application No. 10/188,905 to include the biological activity of not causing an increase in hemoglobin concentration or hematocrit because the both applications employ the same chemically-modified lysine residues or a chemical modification of the N-terminal amino group of the EPO molecule to restore tissue function in mammals. Furthermore, it would be expected that the same chemically-modified EPO of the instant application would similarly have the biological activity of a reduced level of *in vivo* erythropoietic activity compared to erythropoietin as determined by the exhypoxic polycythemic mouse bioassay, tissue protective activity *in vivo* as determined by the middle cerebral occlusion test and crossing endothelial barrier cell barrier/other blood barriers as recited in copending Application No. 10/188,905.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Objections

Claims 7, 14, 16, 18-21 are objected to because they depend from a rejected claim.

Conclusion

Claims 1, 17, 25, 61, 62 and 64 are rejected.

Claims 7, 14, 16, 18-21 are objected to.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Marianne P. Allen/
Primary Examiner, Art Unit 1647

/R. M. D./
Examiner, Art Unit 1647
1/2/09

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/185,841	06/26/2002	Michael Brines	10165-015-999	4194

20583 7590 05/23/2008

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
DEBERRY, REGINA M	
ART UNIT	**PAPER NUMBER**
1647	

MAIL DATE	DELIVERY MODE
05/23/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/185,841	BRINES ET AL.	
	Examiner	Art Unit	
	REGINA M. DEBERRY	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,16-59 and 61-63* is/are pending in the application.

4a) Of the above claim(s) *2-6,8-13,22-24,26,27 and 30-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,14,16-21,25,28,29,61 and 63* is/are rejected.

7)☒ Claim(s) *62* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 07 December 2007 has been entered in full. Claims 2-6, 8-13, 22-24, 26, 27 and 30-59 are withdrawn from consideration as being drawn to a non-elected invention. Claims 15 and 60 were canceled. Claims 1, 14 and 28 were amended. New claims 61-63 were added. The Michael Brines declaration filed 07 December 2007 has been entered.

The supplemental amendment filed 20 February 2008 has been entered in full. Claims 1, 21, 25 were amended. The Second Declaration of Michael Brines filed 20 February 2008 has been entered.

Applicant is reminded that an election of species for an EPO having one or more modified lysine residues and an EPO having a modification of the N-terminal amino (applies to claims 1vii and xvi) and recombinant EPO (applies to claim 28) was made of record. Please see page 2 of the previous Office Action (18 January 2006). Other species embraced by the claims have not been searched.

Claims 1, 7, 14, 16-21, 25, 28, 29 and 61-63 are under examination.

Information Disclosure Statement

The information disclosure statement(s) (IDS) filed 07 December 2007 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Withdrawn Objections And/Or Rejections

The rejection to claims 28, 29 and 60 under 35 U.S.C. 112, second paragraph, as set forth at pages 3-4 of the previous Office Action (27 June 2007), is *withdrawn* in view of the amendment (07 December 2007).

The rejection to claims 1, 7, 14-21 and 25 under 35 U.S.C. 112, first paragraph, scope of enablement (regarding the limitations "one or more modified lysine residues", "modification of the N-terminal amino group" and "restoring the function or viability"), as set forth at pages 4-11 of the previous Office Action (27 June 2007), is *withdrawn* in view of the amendment of 20 February 2007. Claim 1 was amended to recite the limitation "chemically modified" erythropoietin (20 February 2008). The Brines declarations submit that EPO provides tissue protective activity via a separate pathway from the pathway it uses to exert is erythropoietic effects and that chemically modified EPO molecules of the instant invention are non-erythropoietic yet retain tissue protective activity. The Brines declaration states that molecules that do not increase hemoglobin concentration in a mammal are referred to as non-erythropoietic. The Brines declarations submit references which teach that that certain chemically modified EPO (carbamylated, trinitrophenylation, acetylation and succinylation of lysine residues or biotinylation at the N-terminal amino group) proteins have been shown to provide tissue protective activity in the central/peripheral nervous system and other tissue. The Brines declarations submit that the skilled artisan can make chemically modified forms of EPO and discern non-erythropoietic and tissue protective activity without undue experimentation (07 December 2007 and 20 February 2008). In addition, Applicant

submits a Webster's dictionary definition of the term "restore". Applicant argues that restoring the function is to mean wherein EPO may be used to put a cell, tissue or organ back into use. Applicant argues that restoring the function does not require that the claimed cells, tissues and organs are fully returned back to their original state or to regain full function (20 February 2008).

The rejection to claims 28, 29 and 60 under 35 U.S.C. 112, first paragraph, enablement, as set forth at pages 11-13 of the previous Office Action (27 June 2007), is *withdrawn* in view of the amendment, Applicant's arguments, the submitted literature and The Michael Brines declarations, which state that EPO has been shown to provide tissue protective activity in the central/peripheral nervous system and other tissue (07 December 2007).

The rejection to claim 60 under 35 U.S.C. 112, first paragraph, written description, new matter, as set forth at pages 14-15 of the previous Office Action (27 June 2007), is *withdrawn* in view of the amendment (07 December 2007).

Claim Rejections - 35 USC § 102(b)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 28 and 29 remain rejected under 35 U.S.C. 102(b) as being anticipated by Bany-Mohammed et al., Pediatric Research (1996) Vol. 40, No. 3, pages 381-387.

The basis for this rejection is set forth at pages 15-16 of the previous Office Action (27 June 2007).

Bany-Mohammed et al. teach the subcutaneous administration of recombinant human erythropoietin (rhEPO) to rabbits. Erythropoiesis was evaluated in liver and bone marrow (i.e. non-excitable cells). Bany-Mohammed et al. teach that treatment of rhEPO increased erythropoiesis in liver and bone marrow cells and decreased alveolar (i.e. capillary endothelial) thickening. Bany-Mohammed et al. teach that by stimulating erythropoiesis, rhEPO mobilizes non-haem Fe and decreases oxidant injury.

Applicant argues that amended claim 28 does not recite lung tissue. Applicant's arguments have been fully considered but are not deemed persuasive. Claim 28 was amended (07 December 2007) to recite, "a method for protecting, maintaining, enhancing or restoring the function or viability of an erythropoietin-responsive mammalian cell, or its associated cells, tissues or organs comprising administering to a mammal a pharmaceutical composition comprising a therapeutically effective amount of an erythropoietin, wherein said mammalian cell or its associated cells, tissues, or organs is selected from the group consisting of bone, liver, kidney, small intestine, testes, ovary, pancreas and endometrial cells, tissue and organs". The limitations "tissues" and "organs" encompass any type of tissue or organ such as lung tissue or the lung organ.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

NEW CLAIM REJECTIONS/OBJECTIONS

Claim Rejections - 35 USC § 102(b)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 28 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Okuda et al., Digestion 1996, 57:328-332 (Reference submitted by Applicant in Appendix B, 20 February 2008).

Okuda et al. teach that most anemic patients with chronic renal failure have gastric mucosal lesions which improve after the administration of recombinant human erythropoietin (rHuEPO). Okudo et al. teach that rHuEPO has a direct growth-promoting effect on RGM-1 cells (rat gastric mucosal cell), suggesting possible usefulness of rHuEPO administration for the treatment of gastric mucosal damage in patients with chronic renal failure (abstract and page 332). Thus, the instant reference teaches a method for protecting, maintaining, enhancing or restoring the function or viability of an erythropoietin-responsive mammalian cell or its associated cells, tissues or organs **(i.e. small intestine or stomach)** comprising administering to a mammal a pharmaceutical composition comprising a therapeutically effective amount of an erythropoietin.

Claims 28 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Westenfelder et al. Kidney International Vol. 55:808-820, 1999 (Reference submitted by Applicant in Appendix B, 02/20/08).

Westenfelder et al. teach that human, rat and mouse kidney cells express functional erythropoietin (EPO) receptors. Westenfelder et al. teach that EPO stimulates mitogenesis in kidney cells, which may prove beneficial in the repair of an injured kidney while being potentially detrimental to renal malignancies (abstract and pages 814-816. Thus, the instant reference teaches a method for protecting, maintaining, enhancing or restoring the function or viability of an erythropoietin-responsive mammalian cell, or its associated cells, tissues or organs **(i.e. kidney)** comprising administering to a mammal a pharmaceutical composition comprising a therapeutically effective amount of an erythropoietin.

Claims 28 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Mioni et al., Acta Endocrinologica 127:459-65, 1992 (Reference submitted by Applicant in Appendix B, 02/20/08). Moni et al. teach that ruHuEPO exerts a stimulatory effect on testosterone production, suggesting that EPO influences rat Leydig cell steroidogenesis. Moni et al. teach that in male patients undergoing hemodialysis, the treatment with ruHuEPO improved sexual function and increased basal testosterone levels (abstract and page 465). Thus, the instant reference teaches a method for maintaining, enhancing the function or viability of an erythropoietin-responsive mammalian cell, or its associated cells, tissues or organs **(i.e. testes)** comprising administering to a mammal a

pharmaceutical composition comprising a therapeutically effective amount of an erythropoietin.

Claims 28 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Swaak WO 96/14081(Reference submitted by Applicant in Appendix B, 02/20/08). Swaak teaches the use of EPO for the treatment of inflammation. Swaak teaches the use of EPO in treatment of rheumatoid arthritis (RA). Swaak teaches a decrease in morning stiffness and tender joints in RA patients with EPO treatment (abstract, page 3 and page 8). Thus, the instant reference teaches a method for protecting, maintaining, enhancing or restoring the function or viability of an erythropoietin-responsive mammalian cell, or its associated cells, tissues or organs **(i.e. bones)** comprising administering to a mammal a pharmaceutical composition comprising a therapeutically effective amount of an erythropoietin.

Specification

The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection, rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously

incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

The amendment filed 20 February 2008 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: "in which in vivo biological activity was determined by the polycythemic mouse bioassay (Cotes, P.M. and Bangham, D.R. (1961) Nature 191, 1065-1067" (para 0063). Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections-35 USC § 112, First Paragraph, Written Description (New Matter)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 7, 14, 16-21, 25, 61 and 63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The specification as originally filed does not provide support for the invention as now claimed: "..(a) a reduced level of *in vivo* erythropoietic activity compared to native erythropoietin as determined by the exhypoxic polycythemic mouse bioassay, and (b) tissue protective activity *in vivo* as determined by the middle cerebral artery occlusion test.." (claim 1)

Applicant's amendment, filed 20 February 2008, asserts that no new matter has been added. Applicant states that the amendment is supported by the application as originally filed (published as U.S. Publication No. 2003/0104988 on June 5, 2003; "the published application") at page 8, paragraph [0063] of the published application (corresponding to the paragraph bridging page 26 and 27 of the specification as originally filed) incorporates by reference Satake et al; 1990, Biochim. Biophys. Acta 1038:125-9 in its entirety for its description of molecular biological techniques for generating erythropoietin derivatives and testing them for *in vivo* biological activity of erythrocytes *(i.e.,* erythropoietic activity) using the polycythemic mouse bioassay (see Satake, page 126, col. 2: "in vivo biological activity was determined by the exhypoxic polycythemic mouse bioassay", citing Cotes, P.M. and Bangham, D.R. (1961) Nature 191,105-1067).

Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons:

The attempt to incorporate subject matter into this application is ineffective because the incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is

improper. Please see MPEP 608.01(p) and 37 CFR 1.57. The incorporation by reference will not be effective until correction is made to comply with 37 CFR 1.57(b), (c), or (d). If the incorporated material is relied upon to meet any outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance with respect to responding to the objection, rejection, or other requirement for the incorporation to be effective. In no case may the correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier. Any correction inserting material by amendment that was previously incorporated by reference must be accompanied by a statement that the material being inserted is the material incorporated by reference and the amendment contains no new matter. 37 CFR 1.57(f).

Secondly, Applicant is attempting to incorporate by reference twice over (i.e. incorporate by reference to a reference cited in the first reference), which is improper.

Lastly, the specification as originally filed, does not provide a written description for the instant "limitations". That is to say, the *in vivo* erythropoietic activity of chemically modified erythropoietins, as determined by polycythemic mouse bioassay and the *in vivo* tissue protective activity of chemically modified erythropoietins, as determined by the middle cerebral artery occlusion test, was not contemplated at the time of filing and thus results in new matter.

The instant claims now recite limitations which were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as-filed. Applicant is required to cancel the new matter in the response to this Office action. Alternatively, Applicant is invited to provide specific written support for the "limitations" indicated above or rely upon the limitations set forth in the specification as filed.

Claim Objections

Claim 62 is objected to because it depends from a rejected claim.

Matter of Record

Applicant is advised that amending claim 1 as follows would be place claim 1 in allowable form. This amendment would also put dependent claims 7, 14, 16-21, 25, and 61 in condition for allowance. Non-elected claims 2-13, 22-24, 26-27, and 30-59 would need to be cancelled. Pending claims 28-29 and 62-63 would need to be cancelled.

1. A method for protecting, maintaining, enhancing or restoring the function or viability of erythropoietin-responsive mammalian cells, tissues and organs comprising administering to a mammal a pharmaceutical composition comprising a therapeutically effective amount of an erythropoietin having at least one of the following modifications compared to native erythropoietin:

i) at least one or more chemically modified lysine residues or

ii) a chemical modification of the N-terminal amino group of the erythropoietin molecule such that the function or viability of erythropoietin-responsive mammalian cells, tissues and organs is protected, maintained, enhanced or restored without causing an increase in hemoglobin concentration or hematocrit in said mammal.

Chemical modification of lysine residues and the N-terminal amino group of the erythropoietin molecule are discussed at least in paragraphs [0061] and [0076] of Patent Application Publication 2003/0104988 corresponding to the instant application. Chemical modification is distinct from substitution, deletion or insertion of amino acids.

Applicant elected the species of part vii and part xvi in original claim 1. The art has not been searched for other modified erythropoietin embodiments embraced by pending claim 1. However, a cursory review of the art of record indicates that at least part xiv of pending claim 1 (directed to truncations) would be anticipated or obvious over Campana et al. (of record). In addition, at least part ii of pending claim 1 (directed to a reduced or no N-linked carbohydrates), part iii (directed to a reduced carbohydrate content), part iv (a non-mammalian glycosylation pattern) and xv (a reduced number or no O-linked carbohydrates) would be rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. US 6,531,121 B2. The claims of US 6,531,121 B2 are drawn to a method of administering human asialoerythropoietin to protect or maintain the viability of erythropoietin-responsive mammalian cells. The specification of US 6,531,121 B2 teaches asialoerythropoietin as non-erythropoietic (column 3, lines 44-59). The

specification of US 6,531,121 B2 teaches asialoerythropoietin as the removal of N-linked and O-linked glycosylation moieties (column 20, lines 1-30).

Applicant is reminded that amendments after final rejection are not entered as a matter of right. Amendments other than those proposed above or inclusion of other limitations requiring further search and consideration will not be entered.

Conclusion

Claims 1, 7, 14, 16-21, 25, 28, 29, 61 and 63 are rejected.

Claim 62 is objected to.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Marianne P. Allen/
Primary Examiner, Art Unit 1647

RMD
5/21/08

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/185,841	06/26/2002	Michael Brines	10165-015-999	4194

20583 7590 06/27/2007

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EXAMINER	
DEBERRY, REGINA M	

ART.UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
06/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/185,841	BRINES ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *2-6,8-13,22-24,26,27 and 30-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,14-21,25,28,29 and 60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05 April 2007 has been entered.

Status of Application, Amendments and/or Claims

The amendment filed 05 April 2007 has been entered in full. Claims 1-59 are pending. Claims 2-6, 8-13, 22-24, 26, 27, 30-59 are withdrawn. New claim 60 was added. Claims 1, 7, 14-21, 25, 28, 29 and 60 are under examination.

Withdrawn Objections And/Or Rejections

The rejection to claims 28 and 29 under 35 U.S.C. 112, second paragraph, as set forth at pages 3-4 of the previous Office Action (05 October 2006), is *withdrawn in part* in view of Applicant's arguments regarding the claim limitation "not excitable cells, tissues, or organs" (05 April 2007). Please see the 35 U.S.C. 112, second paragraph rejection below.

The rejections claims 1, 7, 14-21 under 35 U.S.C. 112, first paragraph, enablement, as set forth at pages 4-7 of the previous Office Action (05 October 2006), is *withdrawn.*

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28 and 29 (and new claim 60) remain rejected under 35 U.S.C. 112, second paragraph because of the limitation, "do not predominantly comprise excitable cells or tissue".

Applicant argues that a person having ordinary skill in the art at the time the present application was filed would have a clear understanding of the distinction between cells, tissues and organs that are excitable and cells, tissues and organs that are not excitable. Applicant argues that excitable cells contain voltage-gated ion channels for generating action potentials, whereas non-excitable cells do not contain voltage-gated ion channels for generating action potentials. Applicant cites Alberts et al., The Molecular Biology of the Cell and US Patents 5,948,007; 5,702,429 and 5,549,653 as references, which teach excitable cells. Applicant argues that the specification provides examples of non-excitable cells, tissues and organs, such as lung, liver, kidney, small intestine, capillary endothelial, testes, ovary, pancreas or endometrial cells or tissues. Applicant cites page 2, line 21-page 3, line 1.

Applicant's arguments have been fully considered but are not deemed persuasive. The limitation "do not predominantly comprise excitable cells or tissue" is indefinite. The instant specification fails to teach or cite a reference that teaches a cell, tissue or organ that "do not predominantly comprise excitable cells or tissue". The specification fails to teach what that limitation encompasses. For example, the specification does not disclose what percentage of brain or liver or small intestine is excitable cells/tissues and what percentage is non-excitable cells/tissues. The specification does not disclose how to determine these percentages. The references cited by Applicant fail to teach/define cells or tissues that "do not predominantly comprise excitable cells or tissue".

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections-35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 7, 14-21 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method for **protecting, maintaining, enhancing the function or viability of central nervous system tissue or peripheral nervous system tissue** comprising administering to a mammal a pharmaceutical composition comprising a therapeutically

effective amount of an erythropoietin (EPO) **wherein said EPO is biotinylated at free N-terminal amino groups of the EPO molecule or carbamylated at lysine residues of the EPO molecule, such that the function or viability of central nervous system tissue or peripheral nervous system tissue is protected, maintained or enhanced** without causing an increase in hemoglobin concentration or hematocrit in said mammal.

does not reasonably provide enablement for:

a method for protecting, maintaining, enhancing or **restoring the function** or viability of **erythropoietin-responsive mammalian cells, tissues and organs** comprising administering to a mammal a pharmaceutical composition comprising a therapeutically effective amount of an erythropoietin having **at least one or more modified lysine residues or a modification of the N-terminal amino group of the erythropoietin molecule** (elected species), such that the **function** or viability of **erythropoietin-responsive mammalian cells, tissue and organs** is protected, maintained, enhanced or **restored** without causing an increase in hemoglobin concentration or hematocrit in said mammal.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification teaches that biotinylated-EPO (biotinylated at free amino groups) protects p19 cells form serum withdrawal (pages 79-80 and Figure 9). The instant claims are not supported by an enabling disclosure because the specification fails to demonstrate the claimed biological activity of EPO with <u>any type</u> of lysine

residue modification or any type of N-terminal amino group modification. Leist *et al.* (reference of record) teach that EPO with carbamylated lysine residues lacked erythropoietic activity. Satake *et al.* (reference of record) teach that EPO with guanidinated lysine residues showed higher erythropoietic activity. Therefore, modifications in the EPO sequence are critical to the protein's structure/function relationship. Lastly, some of the Examples and Leist et al. teach protecting/maintaining/enhancing the function of central nervous system tissue or peripheral nervous system tissue using EPO, asialoerythropoietin or carbamylated-EPO, but function was not totally restored in these animal models. It could not be predicted that the data presented in the specification (cell culture, animal models) and cited reference would be in any way correlative with the breadth of the instant invention. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

Due to the large quantity of experimentation necessary to demonstrate protection, maintenance, enhancement or restoration of function or viability of all EPO-responsive mammalian cells/tissues/organs by administering to a mammal a pharmaceutical composition comprising a therapeutically effective amount of EPO having at least one or more of any type of lysine residue or N-terminal amino group modification, such that the function or viability of erythropoietin-responsive mammalian cells, tissue and organs is protected, maintained, enhanced or restored without causing an increase in hemoglobin concentration or hematocrit in said mammal, the lack of direction/guidance presented in the specification regarding same, the absence of

working examples directed to same, the complex nature of the invention, the contradictory state of the prior art (see Leist et al. and Sataka et al.), the unpredictability of the effects of lysine mutations on EPO function (see Leist et al. and Sataka et al.), and the breadth of the claims which fail to recite limitations regarding lysine and N-terminal amino group modifications and limitations regarding the types of EPO responsive mammalian cells/tissues/organs, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Applicant cites case law and *In re Wands*, which the Examiner takes no issue with. Applicant argues the specification contains examples in the specification that teach methods of chemically modifying EPO and methods of testing the suitability of the chemically-modified EPO for use in protection, maintenance, enhancement or restoration of the function or viability of EPO-responsive cells, tissue and organs. Applicant cites Examples 2-6 and Fibi et al., U.S. Patent 5,457,089.

Applicant's arguments have been fully considered but are not deemed persuasive. The issue is *not only* if the instant specification is enabled for making the modified EPOs, the issue is *also* whether the modified EPOs *have the claimed biological function*. The instant specification fails to demonstrate the claimed biological activity of EPO with **any type of lysine residue modification** or **any type of N-terminal amino group modification**. Fibi et al. (U.S. Patent 5,457,089) teach the use of muteins of human EPO in the carboxyl terminal region, not the elected species. Example 5 in the instant specification teaches how to make biotinylated-EPO. Figure 9 demonstrates that biotinylated-EPO protect p19 cells form serum withdrawal (pages 79-

80). None of the other Examples are applicable to the argument at hand. None of the Examples teach administering EPO having at least one or more of any type of lysine residue or N-terminal amino group modification to a mammal, such that the function or viability of EPO-responsive mammalian cells, tissue and organs is protected, maintained, enhanced or restored without causing an increase in hemoglobin concentration or hematocrit in said mammal.

Applicant argues that using the assays disclosed in the specification, the skilled artisan, at the time the application was filed, could have determined which EPO derivative could be used with the claimed methods. Applicant argues that performance of these assays was routine and did not require more than ordinary skill. Applicant maintains that simply because the outcome of a specific assay for each modified EPO may not be known in advance, does not make the claimed methods non-enabled since unpredictability of the result of an experiment is not a basis to conclude that the amount of experimentation is undue.

Applicant's arguments have been fully considered but are not deemed persuasive. Undue experimentation is a conclusion reached by weighing all of the Wands Factors. If one skilled in the art can readily anticipate the effect, than there is predictability in the art. In this case, the art is unpredictable based on the evidence provided (Leist et al. and Satake et al.). The evidence for the degree of predictability in the art also relates to the amount of direction needed in the specification. The instant claims are drawn to administering EPO having at least one or more of any type of modification in the lysine residue or any type of modification of the N-terminal amino

group. Without sufficient guidance, the changes which can be made in the structure and still maintain sufficient activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. A considerable amount of time is permissible for the quantity of experimentation needed to make or use the invention based on the disclosure. However this depends on if the invention is routine or if the skilled artisan is given sufficient direction or guidance. In the instant case, the experimentation is not routine. The experimentation would involve making various lysine and N-terminal amino group modifications, then discerning biological activity (protecting, maintaining, enhancing or restoring the function or viability of EPO-responsive mammalian cells, tissues and organs) and then examining hemoglobin concentration and hematocrit levels in a mammal.

Applicant states that they disagree with the Examiner's argument that Leist et al. and Satake et al. (references of record) are contradictory. Applicant argues that Satake et al. illustrate that carbamylation of EPO results in loss of erythropoietic activity of EPO. Applicant maintains that the teachings of Satake are entirely consistent with the teachings of Leist et al., who demonstrate that chemically modified EPO, e.g. carbamylated EPO lacks erythropoietic activity as measured using human cell signaling assays and *in vivo* dosing in animal species. Applicant argues that Leist et al. teach that certain EPO derivatives or variants lack erythropoietic activity but retain their tissue-protective activity. Applicant argues that they provided U.S. Patent Application Publication 2003/0072737 to demonstrate that the EPO derivatives as taught in the presentation have the activities that are required in the claimed method. Applicant

argues that the '737 publication demonstrates the efficacy of carbamylated EPO in protecting neuronal cells in a rabbit spinal cord ischemia assay. Applicant concludes with *In re Wands*.

Applicant's arguments have been fully considered but are not deemed persuasive. Satake et al. teach that **guanidination of amino groups of the lysine residues** yielded derivatives that showed **higher biological activities** *in vitro* than native recombinant human EPO, whereas **amidination of lysine residues** had **no effect on the activity**. Satake et al. teach that **modification of the positive charges of the lysine residues to neutral or negative charges, such as in acetylation, trinitrophenylation, carbamylation or succinylation** cause a significant **loss of recombinant human erythropoietin activity**. Leist *et al.* teach **loss of erythropoietic activity of EPO with carbamylated lysine residues**. Leist et al. teach protection in a cerebral infarct model, improvement of neurological function in a model of spinal cord injury and a model of autoimmune encephalomyelitis using **EPO with carbamylated lysine residues**. Contrary to Applicant's assertion, specific modifications in the EPO sequence are critical to the protein's biological activity. These modifications can either increase or decrease erythropoietic activity as illustrated by Leist *et al.* and Satake *et al.* The specification, the cited references and U.S. Patent Application Publication 2003/0072737 fail to teach the loss of erythropoietic activity of EPO with *any type of lysine residue modification* or *any type of N-terminal amino group modification*. The Examples teach an enhancement of function *in vivo*, using EPO or asialoerythropoietin and Leist et al. teach an enhancement of function *in vivo* using carbamylated-EPO, but

function was not totally restored in the animal models. Thus, the specification, the cited references and U.S. Patent Application Publication 2003/0072737 teach various degrees of function of certain types of erythropoietin-responsive mammalian cells, tissues and organs.

As was stated above, the issue is *not only* if the instant specification is enabled for making the modified EPOs, but also whether the modified EPOs *have the claimed biological function*. The instant claims broadly encompass administering to a mammal, any type of lysine residue modification or any type of N-terminal amino group modification in EPO for protecting, maintaining, enhancing, restoring the function or viability of any type of EPO-responsive mammalian cells, tissue, organ in the absence of working examples and in the presence of art that establishes that specific EPO modifications affect EPO activity and art that establishes that specific EPO modifications affect certain types of erythropoietin-responsive mammalian cells, tissues and organs. It would require an indeterminate quantity of fundamentally unpredictable investigational experimentation of the skilled artisan to determine whether the modifications of EPO, as encompassed by the claims, could be used in an *in vivo* manner (i.e. protecting, maintaining, enhancing, restoring, etc without causing an increasing in hemoglobin concentration or hematocrit) of all EPO-responsive mammalian cells, tissues and organs.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28, 29 and 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to a method for protecting, maintaining, enhancing or restoring the function or viability of an EPO-responsive mammalian cell or its associated cells, tissues, or organs, comprising administering to a mammal, a pharmaceutical composition comprising a therapeutically effective amount of recombinant EPO (elected species), wherein said mammalian cell or its associated cells, tissues, or organs are not excitable cells, tissue, or organs, or do not predominantly comprise excitable cells or tissues.

Shapiro et al., US Patent 4,343,782, teach non-excitable cells, as cells other than muscle and nerve tissue (column 6, lines 49-54). Thus, non-excitable cells or tissue can encompass epithelial cells, immune cells, osteoblasts, connective tissue, secretory cells, fibroblasts, lymphocytes, lung, ovary, kidney, etc. The instant claims are not supported by an enabling disclosure because the instant specification fails to teach a method for protecting, maintaining, or enhancing or restoring the function or viability of any type of non-excitable cell. The Examples teach the administration of EPO or asialoerythropoietin in various animal models. However, the animal models do not

correlate with non-excitable cells, tissues or organs. The instant specification is not enabled for this. The lists of non-excitable cells/tissues are merely illustrative. Furthermore, the instant specification fails to teach or cite a reference that teaches a cell, tissue or organ that *"does not predominantly comprise excitable cells or tissue".* The specification fails to teach what the limitation encompasses. For example, the specification does not disclose what percentage of brain or liver or small intestine is excitable cells/tissues or how to determine these percentages. The specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised the invention.

Due to the large quantity of experimentation necessary to demonstrate that EPO can protect, maintain, enhance or restore the function or viability of all EPO-responsive mammalian cells its associated cells, tissues, or organs that are not excitable cells, tissues, or organs and the large quantity of experimentation necessary to determine how to discern cells, tissues or organs that do not predominantly comprise excitable cells or tissues, the lack of direction/guidance presented in the specification regarding same, the absence of working examples directed to same, the complex nature of the invention, the art which teaches what "excitable tissues" encompass (see Shapiro et al.) and the breadth of the claims which fail to recite limitations regarding EPO-responsive mammalian cell or its associated cells, tissue or organs, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

NEW CLAIM REJECTIONS/OBJECTIONS

Claim Rejections-35 USC § 112, First Paragraph, Written Description (New Matter)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 60 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The specification as originally filed does not provide support for the invention as now claimed: "a method for protecting, maintaining, enhancing or restoring the function or viability of an erythropoietin-responsive mammalian cell or its associated cells, tissue, or organs...selected from the group consisting of **bone, skin...tissues** and **organs**".

Applicant's amendment, filed 05 April 2007, asserts that no new matter has been added and directs support to page 2, page 3, page 9 and the table beginning at page 46 for the written description for the above-mentioned "limitations".

The Examiner has located on pages 2, 3 and 9 of the specification, "the erythropoietin-responsive cell or tissue may be lung, liver, kidney, small intestine, capillary endothelial, testes, ovary, pancreas or endothelial cells or tissues". The Examiner did not locate bone, skin...tissues and organs on pages 2, 3 and 9. The specification on page 46 states, "the following table lists additional exemplary, non-

limiting indications as to the various conditions and diseases amenable to treatment by aforementioned erythropoietins". The table (pages 46-50) teaches the condition/disease and the cell, tissue or organ affected by the condition/disease. The Examiner cannot locate the limitation "a method for protecting, maintaining, enhancing or restoring the function or viability of an erythropoietin-responsive mammalian cell or its associated cells, tissue, or organs...selected from the group consisting of **bone, skin, tissues** and **organs**".

The specification as filed does not provide a written description or set forth the metes and bounds of this "limitations". The instant claims now recite limitations which were not clearly disclosed in the specification as filed, and now changes the scope of the instant disclosure as-filed resulting in new matter.

Applicant is required to cancel the new matter in the response to this Office action. Alternatively, Applicant is invited to provide specific written support for the "limitations" indicated above or rely upon the limitations set forth in the specification as filed.

Claim Rejections - 35 USC § 102(b)

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 28, 29 and 60 are rejected under 35 U.S.C. 102(b) as being anticipated by Bany-Mohammed et al., Pediatric Research (1996) Vol. 40, No. 3, pages 381-387.

The instant claims are drawn to a method for protecting, maintaining, enhancing or restoring the function or viability of an erythropoietin-responsive mammalian cells, or its associated cells, tissues or organs comprising administering to a mammal a pharmaceutical composition comprising a therapeutically effective amount of an erythropoietin, wherein said mammalian cell or its associated cells, tissues, or organs are not excitable cells, tissues, or organs, or do not predominantly comprises excitable cells or tissue.

Bany-Mohammed et al. teach the subcutaneous administration of recombinant human erythropoietin (rhEPO) to rabbits. Erythropoiesis was evaluated in liver and bone marrow (i.e. non-excitable cells). Bany-Mohammed et al. teach that treatment of rhEPO increased erythropoiesis in liver and bone marrow cells and decreased alveolar (i.e. capillary endothelial) thickening. Bany-Mohammed et al. teach that by stimulating erythropoiesis, rhEPO mobilizes non-haem Fe and decreases oxidant injury that depends on the availability of transient metal.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RMD
6/14/07

Marianne P. Allen
MARIANNE P. ALLEN
PRIMARY EXAMINER
AU 1647

6/22/07

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/185,841	06/26/2002	Michael Brines	10165-015-999	4194

7590 10/05/2006

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/185,841	BRINES ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *2-6,8-13,22-24,26,27 and 30-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,14-21,25,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 18 July 2006 has been entered in full. Claims 1-59 are pending. Claims 2-6, 8-13, 22, 23, 24, 26, 27, 30-59 are withdrawn. Claims 1, 7, 14-21, 25, 28 and 29 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

The specification is in compliance with 37 CFR 1.821-1.825 of the Sequence Rules and Regulations.

The rejection to claim 1 under 35 U.S.C. 112, second paragraph, as set forth at pages 5-6 of the previous Office Action (18 January 2006), is *withdrawn* in view of the amendment (18 July 2006).

The rejection to claims 1 and 7 under 35 U.S.C. 103(a) as being unpatentable over Lin, US Patent 5,621,080 in view of Satake *et al.* Biochimica et Biophysica Acta, 1038:125-129 (1990), as set forth at pages 6-8 of the previous Office Action (18 January 2006), is *withdrawn* in view of the amendment (18 July 2006).

Applicant made a species election of an EPO having at least one or more modified lysine residues or a modification of the N-terminal amino group of the erythropoietin molecules (claims 1, 14-21 and 25 read thereon) and recombinant EPO in the reply filed on 28 October 2005. MPEP 803.02 was revised to indicate that if an

Examiner determines that the elected species in a Markush-type claim is allowable, the examination of the Markush-type claim will be extended. The Office is not obligated to extend the search and examination within a Markush claim when the elected or subsequent species is rejected under any of 35 U.S.C. 101, 102, 103 or 112 1st.

Information Disclosure Statement

The information disclosure statement(s)(IDS) filed 18 July 2006 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

Claim Rejections - 35 U.S.C. § 112, Second Paragraph

Claims 28 and 29 remain rejected under 35 U.S.C. 112, second paragraph. The basis for this rejection is set forth at pages 5-6 of the previous Office Action (18 January 2006).

Applicant argues that the specification defines excitable tissues as excitable tissues in the central nervous system, peripheral nervous system or cardiac or retinal tissue. Applicant states that one of ordinary skill in the art would readily identify "not excitable cells, tissues or organs" as those that are not of the central nervous system, peripheral nervous system, cardiac or retina. Applicant argues that numerous examples of "not excitable cells, tissues or organs", are provided on page 21, lines 2-16.

Applicant's arguments have been fully considered but are not deemed persuasive. Page 21, lines 2-16 does not define "not excitable cells, tissues or organs". The expressed exclusion of certain elements implies the inclusion of all other elements not so expressly excluded. The instant specification fails to define the other elements not so expressly excluded in the claim (i.e. all cells, tissues or organs encompassed by "not excitable cells, tissue or organs"). Contrary to Applicant's assertion, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1, 7, 14-21 and 25 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to a method for protecting, maintaining, or enhancing or restoring the function or viability of erythropoietin-responsive mammalian cells, tissues and organs comprising administering to a mammal a pharmaceutical composition comprising a therapeutically effective amount of an erythropoietin having at least one or more modified lysine residues or a modification of the N-terminal amino group of the erythropoietin molecule, such that the function or viability of erythropoietin-

responsive mammalian cells, tissue and organs is protected, maintained, enhanced or restored without causing an increase in hemoglobin concentration or hematocrit in said mammal. The basis for this rejection is set forth at pages 3-5 of the previous Office Action (18 January 2006).

Applicant cites case law and *In re Wands*. Applicant states that modifications to EPO's lysines do impair EPO's erythropoietic activity, but this does not support a finding of unpredictability and lack of enablement. Applicant argues that it was unexpectedly discovered that chemical modifications to EPO that abolished its erythropoietic activity, such as modification of lysines, had no effect on the tissue protective activity of the compounds. Applicant states that these chemically modified EPOs are attractive for use in the instant methods because of their low erythropoietic activity, which results in fewer side effects associated with unwanted increases in hematocrit or blood viscosity. Applicant argues that the teachings coupled with the experimental data disclosed in the specification are sufficient to enable one of skill in the art to practice the instant invention in a human subject. Applicant argues that the efficacy of the claimed methods have since been corroborated as demonstrated by the data attached hereto as Exhibit A. Applicant argues that Exhibit A is a compilation of the data presented as examples in Applicants' copending applications and articles co-authored by the Applicants which utilize the teachings provided in the instant specification to corroborate the disclosed efficacy of the chemically modified EPOs in protecting or maintaining the viability or enhancing the function of a cell, tissue, or organ in a human subject. Applicant

discusses Exhibit A, U.S. Patent Application 10/188,905 and submitted reference Leist *et al.* (Science 2004).

Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons. The Examiner cannot discuss the data of Exhibit A or U.S. Patent Application 10/188,905. Please see matter of record below.

Leist *et al.* (reference submitted by Applicant) teach the recited effects with a **specific lysine modification in erythropoietin (EPO)** (Emphasis added). Leist *et al.* teach the carbamylation of lysines in EPO. Conversely, Satake *et al.* (reference of record) teach that an EPO with guanidination of amino groups of lysine residues yielded derivatives that showed higher biological activities *in vitro* than native recombinant human EPO. Therefore, modifications in the EPO sequence are critical to the protein's structure/function relationship. These modifications can either increase or decrease activity. This is evident from the data of Leist *et al.* and Satake *et al.* Furthermore, the instant examples fail to teach the administration of an EPO with any modification of lysine residues such that the function or viability of EPO-responsive mammalian cells, tissues and organs is protected, maintained, enhanced or restored without causing an increase in hemoglobin concentration or hematocrit in a mammal. Hematocrit and/or hemoglobin levels of mammals receiving EPO with modified lysine residues were not disclosed in the instant application. The instant claims broadly recite an EPO having at least one or more modified lysines residues or a modification of the N-terminal amino group of the EPO molecule in the absence of working examples and in the presence of contradictory art that establishes that EPO modifications affect activity. It would require

an indeterminate quantity of fundamentally unpredictable investigational experimentation of the skilled artisan to determine whether any modified lysine residue or modification of the N-terminal amino group of EPO could be used in an *in vivo* manner (i.e. in a method of EPO administration such that the function or viability of EPO-responsive mammalian cells, tissues and organs is protected, maintained, enhanced or restored without causing an increasing in hemoglobin concentration or hematocrit in said mammal). As plural modifications are introduced, their interactions with each other and their effects on the structure and function of the protein become progressively less predictable. The artisan would accordingly have no resort save trial-and-error experimentation to determine which of the large number of possible structural variants had the functional properties. Such experimentation would be undue for one skilled in this art.

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Matter of Record

The Examiner has not received Exhibit A and thus the data cannot be considered at this time. U.S. Patent Application 10/188,905 was not incorporated by reference in the instant application and thus the data would not have been available. Please see MPEP 608.01(p) and 37 CFR 1.57 regarding "Incorporation by Reference", "Noncompliant Incorporation by Reference" and "New Matter".

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

RMD
9/22/06

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9/28/06

AF

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/185,841	06/26/2002	Michael Brines	10165-015-999	4194

7590 01/18/2006

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 01/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/185,841	BRINES ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *2-6,8-13,22-24,26,27 and 30-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7,14-21,25,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/04,9/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 04 February 2003 and 29 January 2004 has been entered in full. Applicant's election of Group I (claims 1-25 and 28-30) and species election of an EPO having at least one or more modified lysine residues or a modification of the N-terminal amino group of the erythropoietin molecules (claims 1, 14-21 and 25 read thereon) and recombinant EPO in the reply filed on 28 October 2005 is acknowledged. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 2-6, 8-13, 22, 23, 26, 27, 30-59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group (or non-elected species), there being no allowable generic or linking claim. The Election was made **without** traverse in the reply filed on 28 October 2005.

Claims 1, 7, 14-21, 25, 28 and 29 are under examination.

Information Disclosure Statement

The information disclosure statement(s)(IDS) filed 29 January 2004 and 02 September 2004 were received and comply with the provisions of 37 CFR §§1.97 and 1.98. They have been placed in the application file and the information referred to therein has been considered as to the merits.

Sequence Rules

The specification is not in compliance with 37 CFR 1.821-1.825 of the Sequence Rules and Regulations. When the description of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier (SEQ ID NO:), in the text and claims of the patent application.

37 CFR 1.821(a) presents a definition for nucleotide and/or amino acid sequences. This definition sets forth limits in terms of numbers of amino acids and/or numbers of nucleotides, at or above which compliance with the sequence rules is required. Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. Please see MPEP section 2422.01. The specification refers to sequences on page 24, line 21, but does not identify the sequences by their sequence identifiers. Sequences appearing in drawings should be referenced in the corresponding Brief Description thereof. See 37 C.F.R. §1.58(a) and §1.83. Appropriate correction is required.

Appropriate correction is required. Applicant must submit a response to this Office Action and compliance with the sequence rules within the statutory period set for response to this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 7, 14-21 and 25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to a method for protecting, maintaining, or enhancing or restoring the function or viability of erythropoietin-responsive mammalian tissues and organs comprising administering to a mammal a pharmaceutical composition comprising a therapeutically effective amount of an erythropoietin having at least one or more modified lysine residues or a modification of the N-terminal amino group of the erythropoietin molecule.

The instant claims are not supported by an enabling disclosure. Satake *et al.* Biochimica et Biophysica Acta, 1038:125-129, 1990 (reference submitted by Applicant) teach that modification of lysine residues to neutral or negative charges, such as in acetylation, trinitrophenylation, carbamylation or succinylation cause a significant loss of recombinant human erythropoietin activity. Satake *et al.* also teach that the biological activity of recombinant human erythropoietin (EPO) is sensitive to chemical modifications of lysine residues (abstract and page 127, 2nd-3rd paragraph, Table 1 and page 128, Discussion). The instant specification fails to demonstrate biological activity of EPO having at least one or more modified lysine residues, for instance neutral

or negative charges to lysine residues, which are as effective as unmodified EPO. The instant specification fails to teach the administration of the instant EPO to mammals. The specification need not contain an example if the claimed invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without an undue amount of experimentation. Lack of working examples, however is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. In this case, the art is unpredictable based on the evidence provided. One skilled in the art cannot readily anticipate the effect of the claimed invention, the experimentation is not routine and Applicant has provided no guidance.

Due to the large quantity of experimentation necessary to generate the derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention and the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 28 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite because of the recitation "viability of erythropoietin-responsive mammalian; tissues and organs". It appears that the claim should recite "mammalian cells" instead of "**mammalian;**". Appropriate correction is required.

Claims 28 and 29 recite the limitation, "wherein said associated cells, tissue, or organs are **not excitable cells, tissues, or organs, or do not predominantly comprise excitable cells or tissues**". The term "not excitable cells, tissues or organs" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Because the specification fails to define "not excitable cells, tissue or organs", the metes and bounds of the instant claim cannot be determined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lin, US Patent 5,621,080 (reference submitted by Applicant) in view of Satake *et al.* Biochimica et Biophysica Acta, 1038:125-129 (1990)(reference submitted by Applicant).

Lin teaches methods of making recombinant EPO (column 13, line 60-column 14, line 67 and Examples). Lin teaches methods of making recombinant EPO in insect cells (column 36, lines 57-61). Lin teaches methods of administering recombinant EPO to mammals (claims). Lin does not teach methods of administering to a mammal an erythropoietin having at least one or more modified lysine residues or a modification of the N-terminal amino group of the erythropoietin molecule.

Satake et al. teach an embodiment of erythropoietin having at least one or more modified lysine residues or a modification of the N-terminal amino group of the erythropoietin molecule, which is highly active. Sake et al. teach that guanidination of amino groups of the lysine residues yielded derivatives that showed higher biological activities *in vitro* than native recombinant human EPO (abstract, page 127, 4th-5th paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of administering recombinant EPO to mammals as taught by Lin, by modifying EPO with guanidination of the amino groups of lysine residues as taught by Satake with a reasonable expectation of success. The motivation and expected success is provided by Lin and Satake, in that Lin teach that recombinantly made EPO avoids the need to try to purify EPO from natural sources, which could yield unstable biologically inactive preparations of the hormone. Satake et al. teach that the guanidino groups, together with their positive charges, play an important role in the interaction between the receptors and recombinant EPO.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RMD
1/10/06

Marianne P. Allen
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PRIMARY EXAMINER
AU 1647 1/17/06

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/185,841	06/26/2002	Michael Brines	10165-015-999	4194

7590 04/28/2005

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/28/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/185,841	BRINES ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 02 September 2004.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-59 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) 1-59 are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RD

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-25, 28-30, drawn to a method for protecting, maintaining, enhancing or restoring the function or viability of cell comprising administering EPO to a mammal, classified in class 514, subclass 2.

II. Claims 26, 27, 44-46, 50-57 drawn to a pharmaceutical composition comprising EPO, classified in class 530, subclass 350.

III. Claims 31-35, drawn to a method for protecting, maintaining, enhancing or restoring the function or viability of a cell/tissue/organ isolated from a cell comprising administering EPO to the isolated cell/tissue/organ, classified in class 435, subclass 7.1.

IV. Claims 36-39, drawn to a method for restoration of cognitive dysfunction in a mammal comprising administering EPO to a mammal, classified in class 514, subclass 2.

V. Claims 40-43, 47-49, drawn to a method for transcytosis of a molecule across an endothelial cell barrier in a mammal comprising administering a molecule in association with EPO, classified in class 514, subclass 2.

VI. Claims 58-59, drawn to a method for treating a patient having a disease/condition of the CNS and/or peripheral nervous system comprising administering EPO, classified in class 514, subclass 2.

Inventions I, III-VI are unrelated methods. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). The instant specification does not disclose that these methods would be used together. The instant methods are unrelated as they comprise distinct steps and have different functions. For instance, the methodology and materials necessary for discerning transcytosis of a molecule across an endothelial cell barrier comprising administering a molecule associated with EPO differs significantly from a method for treating a patient having a disease/condition of the CNS and/or peripheral nervous system comprising administering EPO. A method for restoration of cognitive dysfunction in a mammal comprising administering to a mammal EPO differs significantly from a method for restoring the function or viability of isolated cells/tissues/organs comprising administering EPO *in vitro*. Therefore, each method is divergent in steps. For these reasons, Inventions I, III-VI are patentably distinct.

Inventions II (product) and I, III-VI (process of use) are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the polypeptide can be used to make antibodies.

Searching the inventions of Groups II and I, III-VI together would impose serious search burden. The inventions of Groups II and I, III-VI have a separate status in the art as shown by their different classifications. Moreover, in the instant case, the search for the EPO compositions and the instant methods are not coextensive. Group II encompasses molecules which are not required for the search of Groups I, III-VI. The search for groups I, III-VI would require a text search for the instant methods in addition to a search for EPO.

The Examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise

proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Claims 29, 32 and 36 are generic to a plurality of disclosed patentably distinct species comprising EPO. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over

the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Claims 1, 2, 4-24, 26, 27, 33, 35, 39, 40, 44, 47, 50-57 are generic to a plurality of disclosed patentably distinct species comprising modified forms of EPO. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

Applicant must elect a modified form of EPO from Claims 1, 26, 33, 39, 40, 44, 47, and the dependent claims that match the elected modified form of EPO.

If Group II is elected; Applicant must also elect a modified form of EPO from claims 50-57.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

Because these inventions are distinct for the reasons given above, have acquired a separate status in the art as shown by their different classification, and the search required for each group is not required for the other groups because each group

requires a different non-patent literature search due to each group comprising different products and/or method steps and/or is recognized divergent subject matter, restriction for examination purposes as indicated is proper.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RMD
4/18/05

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/188,905	07/03/2002	Michael Brines	10165-017-999	9722

20583 7590 10/15/2008

JONES DAY
222 EAST 41ST ST
NEW YORK, NY 10017

EXAMINER	
WANG, CHANG YU	
ART UNIT	**PAPER NUMBER**
1649	

MAIL DATE	DELIVERY MODE
10/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/188,905	BRINES ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35,37,38,44-46 and 50-60* is/are pending in the application.

4a) Of the above claim(s) *1-34 and 44-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35, 37-38, 50-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/8/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 7/8/08 has been entered.

Status of Application/Amendments/claims

2. Applicant's amendment filed 7/8/08 is acknowledged. Claims 36, 39-43 and 47-49 are cancelled. Claims 35, 37, 38, 53 and 54 are amended. Claims 56-60 are newly added. Claims 1-35, 37-38, 44-46, 50-55 and newly added claims 56-60 are pending in this application. Claims 1-34 and 44-46 are withdrawn without traverse (filed on 2/21/06) from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

3. Claims 35, 37-38, 50-55 and new claims 56-60 are under examination with respect to carbamylated EPO as the chemically modified EPO and inflammation as the cause of injury in this office action.

4. It is noted that no declarations dated Oct 5, 2007 (Brines I) and dated Feb 20, 2008 (Brines II) were filed as described on p. 16 or p. 18 of the response. Thus, the arguments related to declarations will not be considered in this office action.

4. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response.

5. Applicant's arguments filed on 7/8/08 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Maintained

In view of the amendment filed on 7/8/08, the following rejections are maintained.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 37 and 39 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/185,841.

Claims 37-39 and 50-55 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 6-7, 11, 13-16, and 31-32 of copending Application No. 10/520,140.

Claims 37-39 and 52-54 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 16-22, and 25 of copending Application No. 11/283/024.

Claims 35-39 and 50-55 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 12-16, 33-34 and 56-58 of copending Application No. 10/612,665.

The above rejections are maintained for the reasons made of record.

On p. 17 of the response, Applicant states that these rejections are provisional so Applicant will not address these rejections. The rejections of the claims under obviousness double patenting as being unpatentable over the claims of copending application Nos. 10/185841, 10/520140,11/283024 and 10/612665 are maintained of record until a terminal disclaimer is filed. It is noted that traversal at the time of indication of allowable subject matter will not be considered timely.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35, 37-38, and 50-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for protecting, maintaining or enhancing the viability of a cell, tissue or organ isolated from a mammalian body comprising exposing said cell, tissue or organ to a pharmaceutical composition

comprising a tissue protective cytokine comprised of a carbamylated erythroprotein, or a method for protection against tissue injury due to inflammation or restoration of tissue function following tissue injury due to inflammation in a mammal by a tissue protective cytokine comprised of a carbamylated erythroprotein, does not reasonably provide enablement for a method for protecting, maintaining or enhancing the viability of a cell, tissue or organ isolated from a mammalian body comprising exposing said cell, tissue or organ to a pharmaceutical composition comprising all chemically modified erythropoietin as broadly claimed, or a method for the protection against tissue injury as broadly claimed; prevention of tissue injury; restoration of tissue and tissue function; or regeneration of tissue and tissue function in a mammal comprising administering all chemically modified erythropoietin or a method of treating and preventing inflammation using all forms of chemically modified erythropoietin as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The rejection is maintained for the reasons made of record and as follows.

First, the method directed to prevention inflammation as recited in independent claims 37 and 56 is not enabled because neither the specification nor the prior art provide guidance as to how to prevent a person from having inflammation caused by any mechanisms or any form of diseases or injury. Any individual has potential to develop any disease, neurological function deficit or injury, which would cause inflammation. However, the instant specification fails to teach how to identify or predict when and which one of us would be susceptible to such disease or inflammation and

predict when we would need administration of a chemically modified erythropoietin (EPO). Neither the specification nor the art teaches that administration of a chemically modified EPO can prevent a person from getting any disease or inflammation caused by any mechanisms. In addition, the cause of the disease or neurological deficits or injury cannot be determined because it can be due to genetic mutation, which is a natural process. The specification fails to provide sufficient guidance as to enable one of skill in the art to practice the invention as it pertains to a method of prevention. Further, Applicant also fails to provide specific guidance as to what specific amount of a chemically modified EPO can be used and thus would be effective to prevent a neurological function deficit or a disease or an injury or inflammation. Thus, a skilled artisan cannot contemplate a right amount to prevent the deficit or disease or to prevent a person from getting the deficit or disease or inflammation.

On p. 18-20 of the response, Applicant argues that no undue experimentation is required to generate the claimed chemically modified EPO. Applicant argues that the specification provides guidance to determine EPO activity in particular, the exhypoxic polycythemic mouse assay and the middle cerebral artery occlusion test, which are routine assays. Applicant argues that the instant specification provides examples of modified tissue-protective EPO with reduced EPO activity. Applicant's arguments have been fully considered but they are not persuasive.

In contrast to Applicant's arguments, the specification fails to provide sufficient guidance as to enable a skilled artisan to practice the claimed invention without undue

experimentation. Although routine experimentation is permitted to show the enablement of the specification, it is under a condition that the status of the prior art is well established and the specification is written in a manner that a skilled artisan can practice the claimed invention without undue experimentation.

However, this is not the case for the instant invention because the specification only teaches that asialoerythropoietin (asialoEPO), or carbamylated EPO, or N^{ε}-carboxy methyl EPO is capable of protecting cells and tissues from tissue injury, such as ischemia or reperfusion injury (i.e. organ transplant or stroke). However, the instant specification fails to teach what other forms of chemical modification on EPOs can maintain the tissue protection activity of the carbamylated EPOs. As previously made of record, it is known in the art that a single amino acid modification on a protein can abolish the protein activity as evidenced by WO 94/24160. Since neither the prior art nor the specification teach what other common structures and characteristics are required for the other forms of chemically modified EPOs to maintain the tissue protection activity, a skilled artisan cannot contemplate what other types of chemical modification on EPOs can still preserve the activity of carbamylated EPOs in tissue protection. In addition, the standards to determine whether the claimed invention is enabled are based on how to make and use the claimed invention not how to guess, test, screen and determine whether the claimed chemically modified EPO would work in the claimed methods. Thus, the disclosure of the specification is deficient and undue experimentation is not merely routine.

"According to In re Bowen, 492 F.2d 859, 862-63, 181 USPQ 48, 51 (CCPA 1974), the minimal requirement is for the examiner to give reasons for the uncertainty of the enablement. This standard is applicable even when there is no evidence in the record of operability without undue experimentation

beyond the disclosed embodiments. See also In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (citing In re Bundy, 642 F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981))" See MPEP 2164.04 [R1].

Furthermore, the invention must be enabled at the time of filing and, therefore, the enablement cannot be supported by later obtained experimental results. In *In re Rasmusson* the Court held that

"If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis". *In re Rasmusson v. SmithKline Beecham Corp.* 75 USPQ2D 1297, p1301.

Claims 35, 37-38, 50-53 and 56 are broadly directed to methods involving the use of the recited chemically modified erythropoietin that is defined only by negative functional limitations and with no or broadly defined structural limitations or to methods for treating and the prevention of any tissue injury or the restoration and/or regeneration of tissue or tissue function. However, the specification fails to provide sufficient guidance as to what common structures and sequences and characteristics are required by these structurally undefined modified EPOs to preserve the activity of tissue protection. Note that

"The 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is

predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971)" See MPEP § 2164.03

On p. 21-22 of the response, Applicant argues that the EPO's tissue-protective activity, regeneration and restoration are supported by the cited references , Junk et al. (PNAS, 2005. 99:10659-10664, Exhibit D), WO2005/032467 (Exhibit C), Webster's collegiate Dictionary 10th edition (Exhibit A) and Lu et al. (J. Neurotrauma 2005. 22:1011-1017, Exhibit B). Applicant's arguments have been fully considered but they are not persuasive.

In contrast, the instant specification does not provide sufficient guidance or evidence as to restore tissue lost to injury or regenerate new tissue or tissue function, which would require evidence of *de novo* tissue synthesis. The sparing of tissue volume following injury indicates only that EPO is capable of reducing inflammation-associated cell death, such as apoptosis or necrosis, but does not go so far as to implicate EPO as being able to induce new cellular growth, which would be necessary to regenerate or restore tissue. It is also noted that the cited references only show the effects of EPO and carbamylated EPO on retinal ischemic injury.

In addition, the specification fails to provide sufficient guidance as to how to prevent any one of us from disease or injury since it is unpredictable when a patient would be suffering from a disease or injury and it is also unpredictable whether administration all forms of chemically modified EPOS can prevent us from suffering a disease or injury. Moreover, the specification fails to establish that all different diseases

caused by different mechanisms can be treated with the same drugs or having the same effects with the same drugs. One treatment for one specific disorder does not apply to another disorder. Thus, it is unpredictable whether the protective effect seen on one condition would be obtainable in other diseases. Accordingly, these claims are not enabled commensurate in scope with the claims because there is no well-established correlation among different diseases. Thus, given the high level of required effect, a high level of evidence showing prevention is also required. The instant specification, however, fails to teach that the administration of the claimed chemically modified erythropoietin molecule – or any EPO molecule for that matter – is able to completely prevent tissue injury. Note that

"The 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971)" See MPEP § 2164.03

A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc, v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held that:

"[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

Thus, in view of the breadth of the claims encompassing the use of molecules with no precise structural requirements, the lack of adequate guidance or working example(s) or

data or evidence supporting a therapeutic effect of EPO molecules on neurological diseases or disorders, or guidance on their use, the unpredictability in the art of treatment of neurodegenerative disease, the unpredictability in the art of biological effects of modifying EPO molecules, and the complex nature of the invention, undue experimentation is required by a skilled artisan to practice the claimed invention. Accordingly, the rejection of claims 35, 37-38, and 50-60 under 35 U.S.C. §112, first paragraph, because the specification does not enable the invention commensurate in scope with the claims is maintained.

8. Claims 35, 37-38, and 50-60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is maintained for the reasons made of record, and as follows.

On p. 29-30 of the response, Applicant argues that instant claims meet the written description requirement because the specification has demonstrated several chemically modified EPOs that retain tissue-protective activity. Applicant further argues that the structure and function of modified EPOs are taught based on SEQ ID NOs:1-4. Applicant further cites Examples 9 and 14 from the New written description guidelines. Applicant's arguments have been fully considered but they are not persuasive.

In contrast, although the specification describes several modified EPOs, the secification fails to demonstrate that these different forms of modified EPOs are able to protect tissue from all forms of injury, diseases or to treat or prevent injury or inflammation or to restore tissue function or regenerate tissues. As previously made of record, the specification only shows that asialoerythropoietin (asialoEPO), or carbamylated EPO, or N^{ε}-carboxy methyl EPO can protect tissue from injury and/or inflammation in animals. However, the scope of the claims encompasses EPO molecules with modifications to particular residues or chemical groups on the EPO molecule that are not limited to molecules as set forth above. Although Applicant is able to modify EPOs in any manner, the specification fails to teach what other specific and common structures or sequences of EPO are required to preserve the activity of carbamylated EPO in tissue protection and thereby can be used in the claimed method. Note that

A definition by function alone "does not suffice" to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." *Eli Lilly*, 119 F.3 at 1568, 43 USPQ2d at 1406. See also *Fiers*, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing *Amgen Inc. v.Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)). An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle &Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004).

Thus, Applicants were not reasonably in possession of the "claimed genus of chemically modified EPOs" and also not in possession the claimed method using the claimed genus of chemically modified EPOs.

Conclusion

9. NO CLAIM IS ALLOWED.

10. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday from 8:30 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang, Ph.D.
September 29, 2008

/Christine J Saoud/
Primary Examiner, Art Unit 1647

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10/188,905	07/03/2002	Michael Brines	10165-017-999	9722

20583 7590 01/08/2008

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EXAMINER	
WANG, CHANG YU	
ART UNIT	**PAPER NUMBER**
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	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application.

4a) Of the above claim(s) *1-34 and 40-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-39 and 50-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/15/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application/Amendments/claims

1. Applicant's amendments filed 6/7/07 & 10/15/07 are acknowledged. Claims 35-36 are amended. Claims 1-55 are pending in this application. Claims 1-34 and 40-49 are withdrawn without traverse (filed on 2/21/06) from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

2. Claims 35-39 and 50-55 are under examination with respect to carbamylated EPO as the chemically modified erythropoietin and inflammation as the cause of injury in this office action.

3. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response.

4. Applicant's arguments filed on 6/7/07 & 10/15/07 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Maintained

In view of the amendments filed on 6/7/07 & 10/15/07, the following rejections are maintained.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the

conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 37 and 39 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/185,841.

Claims 37-39 and 50-55 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 6-7, 11, 13-16, and 31-32 of copending Application No. 10/520,140.

Claims 37-39 and 52-54 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 16-22, and 25 of copending Application No. 11/283/024.

Claims 35-39 and 50-55 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 12-16, 33-34 and 56-58 of copending Application No. 10/612,665.

The above rejections are maintained for the reasons made of record in the office action mailed on 12/07/06, and as follows.

At p. 14 of the response, Applicant requests that the instant provisional rejections be held in abeyance until allowable subject matter is identified. The rejections of the

claims under obviousness double patenting as being unpatentable over the claims of copending application Nos. 10/185841, 10/520140,11/283024 and 10/612665 are maintained of record until a terminal disclaimer is filed. It is noted that traversal at the time of indication of allowable subject matter will not be considered timely.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

Claims 35-39 and 50-55 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for protecting, maintaining or enhancing the viability of a cell, tissue or organ isolated from a mammalian body comprising exposing said cell, tissue or organ to a pharmaceutical composition comprising a tissue protective cytokine comprised of a carbamylated erythroprotein, or a method for the protection against tissue injury due to inflammation or restoration of tissue function following tissue injury due to inflammation in a mammal by a tissue protective cytokine comprised of a carbamylated erythroprotein, does not reasonably provide enablement for a method for protecting, maintaining or enhancing the viability of a cell, tissue or organ isolated from a mammalian body comprising exposing said cell, tissue or organ to a pharmaceutical composition comprising all chemically modified erythropoietin as broadly claimed, or a method for the protection against tissue injury as broadly claimed; prevention of tissue injury; restoration of tissue and tissue function; or

regeneration of tissue and tissue function in a mammal comprising administering all chemically modified erythropoietin as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The rejection is maintained for the reasons made of record in the office action mailed on 12/07/07, and as follows.

At p. 15-17 of the response, Applicant argues that routine experimentation is permitted and working examples are not required to show the enablement of the specification and further cites U.S. v. Telectronics Inc., *Hybritech Inc v. Monoclonal Antibodies, Inc., Nothern Telecom, Inc. v. Datapoint Corp, Philips Petroleum Co. v. United States Steel Corp., DeGeorge v. Bernier, Fields v. Conover, In re Wands, In re Angstadt, and In re Marzocchi* and in support of the arguments. At p. 17-24 of the response, Applicant argues that no undue experimentation is required to make chemically modified EPOs or to identify suitable chemically modified EPOs because chemical modification on proteins is known in the art and the specification provides numerous examples as to how to modify EPOs and identify chemically modified EPOs. Applicant cites the text book "Chemical Reagents for Protein Modification" (CRC press, 1991), WO94/24160, In re Angstadt in support of the arguments. Applicant's arguments have been fully considered but they are not persuasive.

In contrast to Applicant's assertion, the specification fails to provide sufficient guidance as to enable one of skill in the art to practice the claimed invention without undue experimentation. Although working examples are not required and routine

experimentation is permitted to show the enablement of the specification, it is under a condition that the status of the prior art is well established and the specification is written in a manner that a skilled artisan can practice the claimed invention without undue experimentation. However, this is not the case for the instant invention because the specification only teaches that asialoerythropoietin (asialoEPO), or carbamylated EPO, or N^{ε}-carboxy methyl EPO is capable of protecting cells and tissues from tissue injury, such as ischemia or reperfusion injury (i.e. organ transplant or stroke). However, the instant specification fails to teach what other forms of chemical modification on EPOs can maintain the tissue protection activity of the carbamylated EPOs. As previously made of record, it is known in the art that a single amino acid modification on a protein can abolish the protein activity as evidenced by WO 94/24160. Since neither the prior art nor the specification teach what other common structures and characteristics are required for the other forms of chemically modified EPOs to maintain the tissue protection activity, a skilled artisan cannot contemplate what other types of chemical modification on EPOs can still preserve the activity of carbamylated EPOs in tissue protection. Thus, the disclosure of the specification is deficient and undue experimentation is not merely routine.

"According to In re Bowen, 492 F.2d 859, 862-63, 181 USPQ 48, 51 (CCPA 1974), the minimal requirement is for the examiner to give reasons for the uncertainty of the enablement. This standard is applicable even when there is no evidence in the record of operability without undue experimentation beyond the disclosed embodiments. See also In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (citing In re Bundy, 642 F.2d 430, 433, 209 USPQ 48, 51 (CCPA 1981))" See MPEP 2164.04 [R1].

Claims 35-39 and 50-53 are broadly directed to methods involving the use of any chemically modified erythropoietin that is defined only by negative functional limitations

and with no (claims 35, 37-38 and 50-53) or broadly defined (claims 36 and 39) structural limitations. Claims 37-39 and 50-55 are broadly directed to methods for the prevention of any tissue injury or the restoration and/or regeneration of tissue or tissue function. The claims are directed to use of any chemically-modified erythropoietin lacking at least one particular activity normally associated with erythropoietin, such as increasing hematocrit, vasoconstriction, hyperactivating platelets, pro-coagulant activity, or increasing production of thrombocytes. However, the specification fails to provide sufficient guidance as to what common structures and sequences and characteristics are required by these structurally undefined modified EPOs to preserve the activity of tissue protection, indicating that undue experimentation is required by a skilled artisan to explore what other modifications on EPOs can be used in the claimed invention. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made and still maintain activity is unpredictable and the experimentation left to those skilled in the art is extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed invention as currently claimed without further undue experimentation.

At p. 25-27 of the response, Applicant argues that the claimed invention is enabled for protection against tissue injury and prevention of tissue injury caused by diseases and disorders because the specification provides numerous examples. Applicant further submits Exhibit B (Fantacci eta l. PNAS. 2006. 103: 17531-17536) in

support of the arguments. Applicant's arguments have been fully considered but they are not persuasive.

In response, claims 37-39 and 50-55 are broadly directed to methods for the prevention of any tissue injury or the restoration and/or regeneration of tissue or tissue function. The instant specification, however, does not provide sufficient guidance or evidence that the claimed method can restore tissue lost to injury or regenerate new tissue or tissue function, which would require evidence of *de novo* tissue synthesis. The sparing of tissue volume following injury indicates only that EPO is capable of reducing inflammation-associated cell death, such as apoptosis or necrosis, but does not go so far as to implicate EPO as being able to induce new cellular growth, which would be necessary to regenerate or restore tissue. Furthermore, the specification fails to provide sufficient guidance as to how to prevent any one of us from disease or injury since it is unpredictable when a patient would be suffering from a disease or injury and it is also unpredictable whether administration all forms of chemically modified EPOS can prevent us from suffering a disease or injury. Thus, given the high level of required effect, a high level of evidence showing prevention is also required. The instant specification, however, fails to teach that the administration of the claimed chemically modified erythropoietin molecule – or any EPO molecule for that matter – is able to completely prevent tissue injury.

"The 'predictability or lack thereof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of

predictability. In particular, the court in In re Marzocchi, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971)" See MPEP § 2164.03

A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc, v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held that:

"[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

Thus, in view of the breadth of the claims encompassing the use of molecules with no precise structural requirements, the lack of adequate guidance or working example(s) or data or evidence supporting a therapeutic effect of EPO molecules on neurological diseases or disorders, or guidance on their use, the unpredictability in the art of treatment of neurodegenerative disease, the unpredictability in the art of biological effects of modifying EPO molecules, and the complex nature of the invention, undue experimentation is required by a skilled artisan to practice the claimed invention. Accordingly, the rejection of claims 35-39 and 50-55 under 35 U.S.C. §112, first paragraph, because the specification does not enable the invention commensurate in scope with the claims is maintained.

7. Claims 35-39 and 50-53 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is maintained for the reasons made of record in the office action mailed on 12/07/06, and as follows.

At p. 29-30 of the response, Applicant argues that the instant claims 35-39 and 50-55 meet the written description requirement because the specification has disclosed structural and functional characteristics of chemically modified EPOs. Applicant further cites *Invitrogen v. Clontech Lab* in support of the arguments. Applicant's arguments have been fully considered but they are not persuasive.

As previously made of record and the discussion above, the specification only shows that asialoerythropoietin (asialoEPO), or carbamylated EPO, or N^6-carboxy methyl EPO can protect tissue from injury and/or inflammation in animals. However, the scope of the claims encompasses EPO molecules with modifications to particular residues or chemical groups on the EPO molecule that are not limited to molecules as set forth above. Although Applicant is able to modify EPOs in any manner, the specification fails to teach what other specific and common structures or sequences of EPO are required to preserve the activity of carbamylated EPO in tissue protection and thereby can be used in the claimed method. Note that

A definition by function alone "does not suffice" to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." *Eli Lilly*, 119 F.3 at 1568, 43 USPQ2d at 1406. See also *Fiers*, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing *Amgen Inc. v.Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)). An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle &Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004).

In contrast, the specification provides an invitation for others to discover a representative number of species that can be used in the claimed method, or to discover what constitutes any particular portion of the structure that must be conserved, with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics that can be used the claimed method. Thus, Applicants were not reasonably in possession of the "claimed genus of chemically modified EPOs" that can be used in the claimed method.

Conclusion

8. NO CLAIM IS ALLOWED.

9. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

10. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday and every other Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang, Ph.D.
December 27, 2007

CHRISTINE J. SAOUD
PRIMARY EXAMINER

Christine J. Saoud

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/188,905	07/03/2002	Michael Brines	~~KW00-002B0Z~~-US	9722

7590 12/07/2006

FREDERICK J HAMBLE
712 KITCHAWAN ROAD
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10165-017

EXAMINER	
BALLARD, KIMBERLY A	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 12/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/188,905	BRINES ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

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Status

1)☒ Responsive to communication(s) filed on *24 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55* is/are pending in the application..

4a) Of the above claim(s) *1-34 and 40-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-39 and 50-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/21/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

Claims 36, 37 and 39 have been amended as requested in the amendment filed on September 21, 2006. Following the amendment, claims 1-55 are pending in the instant application.

Claims 1-34 and 40-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim.

Accordingly, claims **35-39** and **50-55** are under examination in the instant action. The claims are examined to the extent of the following elected species: carbamylated EPO (which reads upon sub-generic element vii in claims 36 and 39) as the chemically modified erythropoietin species and inflammation as the cause of injury species.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

In view of Applicant's amendments to the claims and further in view of the response filed September 21, 2006, for purposes of prior art, the effective filing date for instant claims 35-39 and 50-55 is granted as the filing date of application 09/753,132, now US Patent No. 6,531,121, to which the instant application claims benefit, the date of **December 29, 2000**.

Withdrawn Objections and/or Rejections

The rejection of claims 37-39 and 50-55 under 35 U.S.C. 112, first paragraph (new matter), as set forth at pp. 3-4 of the previous office action (03/21/2006) is withdrawn in view of applicant's amendments to the claims.

The rejection of claims 37-39 and 50-55 under 35 U.S.C. 112, second paragraph, as set forth at p. 4 of the previous office action (03/21/2006) is withdrawn in view of applicant's amendments to the claims.

The rejection of claims 35-36 under 35 U.S.C. 102(b), as set forth at p. 9 of the previous office action (03/21/2006) is withdrawn in view of applicant's amendments to the claims.

Applicant's arguments, see p. 23 in particular, filed 09/21/2006, with respect to claims 37-39 and 50-54 have been fully considered and are persuasive. The 103(a) rejection of claims 37-39 and 50-54, as being obvious over Brines et al. (2000), in view of Satake (1990), and Ogden (1989), has been withdrawn.

Applicant's arguments, see p. 24 in particular, filed 09/21/2006, with respect to claims 37-39 and 50-54 have been fully considered and are persuasive. The 103(a)

rejection of claims 37-39 and 50-54, as being obvious over US Patent 5,614,184 to Sytkowski et al., in view of Satake (1990), and Ogden (1989), has been withdrawn.

Maintained Claim Rejections

Obviousness-Type Double Patenting

The provisional rejection of instant claims 37 and 39 on the ground of nonstatutory obviousness-type double patenting over claim 1 of copending Application No. 10/185,841 is maintained for reasons of record set forth in the previous office action (03/21/2006).

The provisional rejection of instant claims 37-39 and 50-55 on the ground of nonstatutory obviousness-type double patenting over claims 6-7, 11, 13-16, 31-32 and 49-50 of copending Application No. 10/520,140 is maintained for reasons of record set forth in the previous office action (03/21/2006).

The provisional rejection of instant claims 37-39 and 52-54 on the ground of nonstatutory obviousness-type double patenting over claims 1, 16-22 and 25 of copending Application No. 11/283,024 is maintained for reasons of record set forth in the previous office action (03/21/2006).

Applicant requests that the instant provisional rejections be held in abeyance until allowable subject matter is identified. Accordingly, the provisional rejections are maintained and held in abeyance.

New Claim Rejections and/or Objections, Necessitated by Amendment

Obviousness-Type Double Patenting

Claims 35-39 and 50-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 12-16, 33-34 and 56-58 of copending Application No. 10/612,665. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '665 application contains claims to a method for protecting, maintain or enhancing the viability of a cell, tissue or organ isolated from a mammalian body comprising exposing said cell, tissue or organ to a pharmaceutical composition (such as in claim 1) comprising a modified erythropoietin molecule that lacks at least one erythropoietic activity (claim 56). The specification indicates that mammals include humans. Further, the '665 application recites the use of pharmaceutical compositions comprising the modified erythropoietin molecule lacking specific erythropoietic activities for the protection against and prevention of a tissue injury as well as the restoration of and rejuvenation of tissue and tissue function in a mammal (claim 57), wherein the injury is caused by inflammation among many other things (claim 58). Noted limitations which serve to define the potential uses for and modifications of the erythropoietin molecule contained within the pharmaceutical composition to be used in the recited methods

include: responsive mammalian cells (claims 12 and 13), traversing endothelial cell barriers (claims 14 and 15), chemical modifications (claim 16), carbamylation of at least one lysine reside (claim 33), and specific carbamylated species (claim 34). Accordingly, the '665 application renders obvious instant claims 35-30 and 50-55.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

Claims 35-39 and 50-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for protecting, maintaining or enhancing the viability of a cell, tissue or organ isolated from a mammalian body comprising exposing said cell, tissue or organ to a pharmaceutical composition comprising a tissue protective cytokine comprised of a chemically modified erythropoietin as indicated in claims 54 and 55, or a method for the protection against tissue injury due to inflammation or restoration of tissue function following tissue injury due to inflammation in a mammal comprising administering to the mammal a tissue protective cytokine comprised of a chemically modified erythropoietin as indicated in claims 54 and 55, does not reasonably provide enablement for a method for protecting, maintaining or enhancing the viability of a cell, tissue or organ isolated from a mammalian body comprising exposing said cell, tissue or organ to a pharmaceutical composition comprising any chemically modified erythropoietin as broadly claimed, or a method for the protection against tissue injury as broadly claimed; prevention of tissue

injury; restoration of tissue and tissue function; or regeneration of tissue and tissue function in a mammal comprising administering any chemically modified erythropoietin as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

Claims 35 and 36 are drawn to an *ex vivo* method of protecting, maintaining or enhancing the viability of isolated human cells, tissues or organs, comprising exposing said tissue to a pharmaceutical composition comprising a tissue protective cytokine that lacks at least one activity normally associated with erythropoietin. Claims 37-39 and 50-55 are drawn to an *in vivo* method of protecting against tissue injury, prevention of tissue injury, restoration of tissue and tissue function, or regeneration of tissue and tissue function in a mammal comprising administering to the mammal a tissue protective cytokine that lacks at least one activity normally associated with erythropoietin. The claims further recite that the chemically modified erythropoietin is one of thirteen recited modified species of erythropoietins, ranging from an erythropoietin having no sialic acid moieties (sub-generic element (i)) to a truncated erythropoietin (sub-generic element

(xiii)). A number of causes of the tissue injury are further recited (as in claim 38), ranging from more "basic" causes such as stroke, ischemia, myocardial infarction, radiation damage and inflammation, to much more complicated causes such as multiple sclerosis, seizure disorder, neurodegenerative disease (including, for example, Alzheimer's disease, Parkinson's disease, ALS, Creutzfeldt-Jakob disease), AIDS dementia, mood and anxiety disorder, alcoholism, and even aging (age-related loss of cognitive function), cerebral palsy and autism to name a few. Similarly, the scope of the tissues to be treated is quite broad (claims 52 and 53).

The nature of the invention is the demonstration that the administration of – or exposure of cells to – erythropoietin, or a particular chemically-modified form of erythropoietin (EPO) such as asialoerythropoietin (asialoEPO), or carbamylated EPO or asialoEPO, is capable of protecting cells and tissues from tissue injury, such as ischemia or reperfusion injury, as may occur during organ transplant or stroke, for example. The instant specification demonstrates the following: pretreatment with chemically modified EPO, such as carbamylated EPO, carbamylated asialoEPO, or N^{ε}-carboxy methyl EPO, in mice subjected to water intoxification (which can result in brain edema) results in improved scores on neurological tests (Example 4); EPO can cross the blood-brain barrier (Example 5) and the blood-eye barrier (Example 8); pretreatment with EPO can maintain the function of rat hearts prepared for transplantation (Example 6) and also protect myocardium from ischemic injury (Example 7); rats subjected to blunt brain trauma have improved cognitive function when administered EPO several days following injury (Example 9); EPO pretreatment reduced the toxicity (measured as

a delay in time till death) of kainate-induced neurotoxicity in rats (Example 10); EPO treatment improved motor performance in animals subjected to spinal cord injury (Examples 11.1 and 11.2); EPO treatment decreased brain tissue loss and inflammation associated with middle cerebral artery occlusion (MCAO, an animal model of stroke and/or ischemia) in rats (Example 12.1); in an experimental allergic encephalomyelitis (EAE) model (an animal model of multiple sclerosis) using autoimmune disease-prone female Lewis rats, EPO treatment delayed the onset of and severity of disease when administered 3 days after myelin basic protein (MBP) inoculation (Example 12.2); and finally, in an *in vitro* model, incubation of mixed neuron-glia cultures with EPO decreased neuronal death-induced TNF production (a measure of inflammation, as TNF is a pro-inflammatory cytokine) ([00276-00277]). The state of the art also recognizes many of these neuroprotective effects in animals administered EPO, see Brines et al. (2000) *Proc Natl Acad Sci USA*, 97(19): 10526-10531. The art also recognizes that, with the exception of the kainate neurotoxicity model, the disease and/or injury models employed in the instant disclosure are all associated either directly or indirectly with inflammation or immune-mediated inflammatory responses (see Brines et al., p. 10531).

However, claims 35-39 and 50-53 are broadly directed to methods involving the use of any chemically modified erythropoietin that is defined only by negative functional limitations and with no (claims 35, 37-38 and 50-53) or broadly defined (claims 36 and 39) structural limitations. Moreover, claims 37-39 and 50-55 are broadly directed to methods for the prevention of any tissue injury or the restoration and/or regeneration of tissue or tissue function. Note that with regard to the claim breadth, the standard under

35 U.S.C. § 112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the enablement scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest reasonable interpretation of claims 35-36 is of a method encompassing the use of any chemically-modified erythropoietin lacking at least one particular activity normally associated with erythropoietin, such as increasing hematocrit, vasoconstriction, hyperactivating platelets, pro-coagulant activity, or increasing production of thrombocytes. The broadest reasonable interpretation of claims 37-39 and 50-53 is of a method of protecting against or preventing any tissue injury *in vivo*, or a method of restoring or regenerating new tissue or tissue function *in vivo*, using any modified erythropoietin so long as it lacks at least one commonly associated erythropoietic activity, or of prevention of any tissue injury using a carbamylated erythropoietin, as in claims 54 and 55.

While the skill level in the art is high, the level of predictability is low. The working examples provided in the instant specification are limited to demonstrating: 1) the ability of EPO to cross endothelial cell barriers, 2) the effectiveness of EPO or specifically modified EPO species to reduce tissue injury associated with transplantation, reperfusion/ischemia, or physical/chemical injury, 3) the ability of EPO to reduce inflammation associated with injury, and 4) the ability of EPO to improve tissue function following injury and/or reduce the negative consequences of injury on particular cognitive or motor functions. The instant specification, however, does not

provide sufficient guidance or evidence that the claimed method can restore tissue lost to injury or regenerate new tissue or tissue function, which would require evidence of *de novo* tissue synthesis. The sparing of tissue volume following injury indicates only that EPO is capable of reducing inflammation-associated cell death, such as apoptosis or necrosis, but does not go so far as to implicate EPO as being able to induce new cellular growth, which would be necessary to regenerate or restore tissue. Similarly, the art recognizes that EPO administration is able to reduce the extent of tissue damage following insult or injury, but EPO does not in fact cause the production, synthesis, or regeneration of new tissues (see Brines et al. (2000)). Thus the scope of the claimed invention is not commensurate with the teachings of the instant specification or with teachings in the prior art. Furthermore, "prevention" is understood in the art to encompass total protection from disease or injury. Thus, given the high level of required effect, a high level of evidence showing prevention is also required. The instant specification, however, fails to teach that the administration of the claimed chemically modified erythropoietin molecule – or any EPO molecule for that matter – is able to completely prevent tissue injury.

Additionally, as discussed above, the subject matter broadly encompasses treatment of diverse neurological ailments ranging from neurodegenerative diseases such as Alzheimer's disease, Creutzfeldt-Jakob disease, ALS and Parkinson's disease, to conditions such as memory loss, age-related cognitive decline, anxiety and mood disorders, to inherited diseases such as Leigh's disease, to diseases of unknown or uncertain etiology such as autism, cerebral palsy and alcoholism, and many other

diseases, disorders and conditions. The instant specification fails to provide any evidence or sound scientific reasoning to support a conclusion that the working examples, which pertain to the reduction of tissue injury or inflammation associated with injury, could be successfully extrapolated to methods of treating injury caused by multifaceted neurodegenerative or neurlogical diseases or conditions such as those listed above and in claim 38. The only examples provided in the instant specification pertain to treatment of acute tissue injury. However, all of the neurodegenerative diseases and most of the neurological conditions and disorders recited in instant claim 38 are known to be chronic in nature and have complicated pathologies and etiologies. Moreover, neurodegenerative diseases such as Parkinson's, Alzheimer's, and Huntington's disease have proven recalcitrant to treatment in the art, even when treatment involves the use of anti-inflammatory or anti-oxidant agents (see for example, Steece-Collier et al. *Proc Natl Acad Sci USA*, 2002; 99(22): 13972-13974; Diaz Brinton & Yamazaki, *Pharmaceutical Res*, 1998; 15(3): 386-398; Feigin & Zgalijardic, *Curr Opin Neurol*, 2002; 15: 483-489). One would have no basis for concluding that administration of any erythropoietin, even the particular chemically modified EPO species disclosed in Example 4 of the instant specification, would have any effect on protecting tissue injury in any or all these chronic neurodegenerative conditions because such assertion is not supported by any factual evidence of record. Hence, it would require undue experimentation on the part of a skilled practitioner to discover how to practice the full scope of the instant invention, as currently claimed.

Additionally, the scope of the claims includes the use of modified erythropoietin molecules that are defined only by negative limitations and broad structural limitations, such as in instant claims 36 and 39, which recite vague guidelines as to how the erythropoietin is to be chemically modified. For example, the chemically erythropoietin may have one or more modified lysine residues or a modification of the N-terminal amino group of the molecule (element vii), or have at least one modified tyrosine residue (element viii), aspartic acid or glutamic acid residue (element ix), or tryptophan residue (element x), or is a truncated erythropoietin (element xiii). In the case of the modified residues or groups, "modification" includes substitution and/or deletion of the residue in addition to chemical modifications. However, it is also known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function or structure. For example, WO 94/24160 document by Boissel et al. (published October 27, 1994) note that replacement of particular residues, such as Lys140, Arg143, Ser146, Asn147 or Lys154, with alanine resulted in an EPO molecule with significantly increased (3-fold) biological activity, whereas replacement of a tyrosine residue (Tyr156) with alanine resulted in a molecule with slightly decreased biological activity (see p. 69, lines 2-11, and Figures 19-22). Boissel et al. additionally note that while an EPO molecule lacking N-linked carbohydrates may have full *in vitro* biological activity, it has drastically shortened half-life *in vivo* (see p. 40, lines 8-16), and thus would not be predicted to be capable of therapeutic use. The art thus recognizes unpredictability in the biological activity of modified EPO molecules according to recited modifications encompassed by

the instant claims in that certain modifications, such as substitution of particular amino acid residues, result in EPO molecules with enhanced biologically activity rather than the desired decreased or deficient biological activity. It would thus appear that certain modifications recited in claims 36 and 39, for example, would be potentially be inoperative as they are currently broadly recited, requiring undue experimentation of the skilled artisan to determine which particular modifications are effective for practicing the claimed methods.

Therefore, in view of the breadth of the claims encompassing the use of molecules with no precise structural requirements, the lack of adequate guidance or working example(s) or data or evidence supporting a therapeutic effect of EPO molecules on neurological diseases or disorders, or guidance on their use, the unpredictability in the art of treatment of neurodegenerative disease, the unpredictability in the art of biological effects of modifying EPO molecules, and the complex nature of the invention, one of skill in the art would find that undue experimentation would be required to practice the claimed invention.

Claims 35-39 and 50-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Factors to be considered when determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. (Written description guidelines, Federal Register, vol. 66, no. 4, January 2002, 9.1106, column 2).

The claims are directed to *ex vivo* and *in vivo* treatment methods involving exposing an isolated cell, tissue or organ to, or administering to a mammal, a tissue protective cytokine comprised of a chemically modified erythropoietin that lacks at least one biological activity normally associated with erythropoietin. Because the methods require the use of EPO molecules that are broadly defined only by a negative functional limitation, the claims encompass a method of using a genus of EPO molecules.

A description of a genus may be achieved by means of a recitation of a representative number of members, defined by structure and/or function, falling within the scope of the genus, or of a recitation of structural and/or functional features common to the genus, which features constitute a substantial portion of the genus. Applicant has disclosed several chemically modified EPO molecules that were shown to be effective *in vivo* for reducing the negative consequences of injury and/or inflammation in animals (Example 4 and 11). However, the scope of the claims encompasses EPO molecules with modifications to particular residues or chemical groups on the EPO molecule that are not limited to the elected species, carbamylated EPO, or to the particular species of Examples 4 and 11. For example, the instant

specification discloses that the erythropoietin molecules may be modified in any number of ways including, but not limited to, guanidination, amidination, carbamylation, trinitrophenylation, acetylation, succinylation, nitration, or modification of argnine, lysine, tyrosine, tryptophan, or cysteine residues or carboxyl groups by proteolysis, removal of amino groups, and/or mutational substitution of the residues ([0066]). The scope of the claims therefore broadly encompasses any number or modified EPO molecules which are defined only in that they lack a particular biological activity, such as increasing hematocrit, vasoconstriction, hyperactivating platelets, pro-coagulant activity, or increasing thrombocyte production.

Thus, the scope of the claims includes numerous structurally different amino acid molecules, and the genus is highly variable because a significant degree of structural variation is permitted. Structural features that could distinguish the instantly claimed modified erythropoietin molecules in the genus from other molecules in the nucleic amino acid class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Accordingly, there is no means by which the artisan, given any of these EPO molecules, would know whether it was a member of the genus that could be used in the claimed methods. The instant disclosure of the several specific modified EPO species does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. Therefore, the claims are directed to subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed genus of modified EPO molecules.

Claim Objections

Claims 36, 38 and 39 are objected to because of the following informalities: The claims recite non-elected species. Appropriate correction is required.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on M-F 9 AM - 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

Kimberly Ballard, Ph.D.
November 29, 2006

ELIZABETH KEMMERER
PRIMARY EXAMINER

UNITED STATES PATENT AND TRADEMARK OFFICE

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10165-017

EXAMINER	
BALLARD, KIMBERLY A	
ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 03/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/188,905	BRINES ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-39 and 50-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35-39 and 50-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *09/02/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The amendment filed 21 February 2006 has been entered in full.

Election/Restrictions

Applicant's election without traverse of Group II (claims 35-39) and species election of a carbamylated EPO (sub-generic element vii in claims 36 and 39 read thereon) as the chemically modified erythropoietin and inflammation as the cause of injury in the reply filed on 21 February 2006 is acknowledged.

Claims 1-34 and 40-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 21 February 2006.

Claims 50-55 have been added in the amendment dated 21 February 2006. Accordingly, claims **35-39** and **50-55** are pending and under examination in this office action.

Information Disclosure Statement

A signed and initialed copy of the information disclosure statement (IDS) submitted 2 September 2004 is enclosed in this action. Reference DO cited on the IDS was lined through because it did not provide a publication date and therefore is considered improper. The printer has been instructed not to print this citation.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-39 and 50-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

Claim 37 has been amended to specifically recite a method for the *rejuvenation* of tissue and tissue function in a mammal (emphasis added), which is not supported in the specification as originally filed. Dependent claims 38-39 and 50-55 are included in this rejection in that the method is a limitation of these claims by virtue of their dependency, although the method is not specifically recited separately therein.

The best support for this method appears in paragraph [0017], which discloses "...a method is provided for the protecting, maintaining, enhancing or restoring the function or viability of responsive mammalian cells and their associated cells, tissues and organs..." However, there is no description of methods pertaining to the rejuvenation of cells, tissues, or tissue function. Rejuvenation implies the process of renewing, refreshing, or restoring youth or youthful appearance. While rejuvenation may be similar to restoration, the claim as recited clearly differentiates between a

method for restoration of tissue and tissue function ***or*** a method for the rejuvenation of tissue and tissue function. While the instant disclosure provides support for the former, no such discussion of methods for rejuvenation appears in the specification. Therefore, the specification as originally filed does not have adequate written description for the claimed invention reciting methods of rejuvenation.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite in the phrase "rejuvenation" in reference to the rejuvenation of tissue and tissue function". The phrase "rejuvenation" is vague and indefinite because the specification does not define "rejuvenation" and it is not clear what rejuvenated tissue or tissue function would constitute. The metes and bounds of the claim thus cannot be ascertained.

Dependent claims 38-39 and 50-55 are similarly rejected in that the phrase "rejuvenation of tissue and tissue function" is a limitation of these claims by virtue of their dependency, although the phrase is not specifically recited separately therein.

Priority

According to the instant specification, priority is being claimed to both US Patent Application No. 09/753,132, filed 29 December 2000, now US Patent No. 6,531,121,

and to PCT Application PCT/US01/49479 (filed 28 December 2001) which claims benefit of provisional application 60/259,245 filed on 29 December 2000. Support for the subject matter of claim 36 specifically pertaining to carbamylated erythropoietins (i.e., an erythropoietin having at least one or more modified lysine residues or a modification of the N-terminal amino group) is found only in PCT/US01/49479, and not in 09/753,132 or 60/259/245, and therefore this claim has the effective filing date of 28 December 2001. The effective filing date for claim 37 and dependent claims 38, 39 and 50-55 cannot be properly determined at this time because they contain new matter as noted *supra*. Accordingly, claims 37-39 and 50-55 are assigned the effective filing date of 3 July 2002, that of the instant application, for the purpose of examination until said claims are amended to negate the new matter rejection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Omum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 37 and 39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 10/185,841. Although the conflicting claims are not identical, they are not patentably distinct from each other because claim 1 of the '841 application is drawn to a method for protecting, maintaining, enhancing or restoring the function or viability of tissues and organs comprising administering to a mammal a therapeutically effect amount of a pharmaceutical composition comprising an erythropoietin having at least one or more modified lysine residues or a modification of the N-terminal amino group of the erythropoietin molecule. Because the chemical modification is the same in both applications, it would be expected that the chemically-modified erythropoietin of the '841 application would similarly lack at least one erythropoietic activity as instantly recited. Thus, the '841 application renders obvious instant claims 37 and 39.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 37-39 and 50-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 6-7, 11, 13-16, and 31-32 of copending Application No. 10/520,140. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '140 application contains claims drawn to methods for treating inflammation in a mammal

comprising administering a tissue protective cytokine (claim 6), with noted claim limitations including: the tissue protective cytokine lacks at least one erythropoietic activity (claim 7), the tissue protective cytokine is an erythropoietin comprising at least one or more modified lysine residues or a modification of the N-terminal amino group of the molecule (claim 11, vii), the tissue protective cytokine is capable of traversing an endothelial cell barrier (claim 13), the cell barrier is selected from blood-brain, blood-eye, blood-testis, blood-ovary, and blood-uterine barriers (claim 14), the responsive cells, tissues and/or organs in the mammal are selected from neurons, muscles, heart, lung, liver, kidney, small intestine, adrenal cortex, adrenal medulla, capillary, endothelial, testes, ovary, endometrial, and stem cells (claim 15), wherein the responsive cells further comprise more specific cell types (claim 16), the tissue protective cytokine is an erythropoietin having at least one carbamylated lysine residue (claim 31), and wherein the carbamylated erythropoietin is selected from a group of specific erythropoietin molecules (claim 32). Thus, the '140 application renders obvious instant claims 37-39 and 50-55.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 37-39 and 52-54 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 16-22, and 25 of copending Application No. 11/283/024. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '024 application

contains claims drawn to methods for protecting or maintaining the viability of a cell, tissue or organ comprising administering to a mammal a pharmaceutical composition comprising an erythropoietin or a tissue protective cytokine, with notable claim limitations including: the cells comprise neuronal, retinal, muscle, heart, lunch, liver, kidney, small instestine, adrenal cortex, adrenal medulla, capillary, endothelial, testes, ovary, endometrial, and stem cells (claim 16), wherein the mammalian cells further comprise more specific cell types (claim 17), wherein the trauma or injury is caused by inflammation (claim 18), wherein the erythropoietin is chemically modified (claim 19), wherein the tissue protective cytokine lacks at least one erythropoietic activity selected from a group of activities (claim 20) and it is chemically modified (claim 21), wherein the chemically modified erythropoietin has at least one or more modified lysine residues (vii) or at least one modification of the N-terminal amino group (viii) (claim 22), and wherein the tissue protective cytokine is an erythropoietin having at least one carbamylated lysine residue (claim 25). Thus, the '024 application renders obvious instant claims 37-39 and 52-54.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 35-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Satake et al. 1990, *Biochimica et Biophysica Acta*, 1038: 125-129 (as listed on Applicant's IDS filed 9/2/04).

Claims 35-36 are drawn to a method for protecting, maintaining or enhancing the viability of a cell, tissue or organ isolated from a mammalian body comprising exposing said cell, tissue or organ to a pharmaceutical composition comprising a tissue protective cytokine comprised of a chemically modified erythropoietin that lacks at least one erythropoietic activity, and wherein the chemically modified erythropoietin has at least one or more modified lysine residues or a modification of the N-terminal amino group.

Satake et al. teaches modifications of recombinant human erythropoietin (rHuEPO), such as rHuEPO that has been carbamylated by potassium cyanate, thereby modifying of lysine residues (see p. 126, 1st column and Table 1). Satake teaches that carbamylation of rHuEPO results in a significant loss of *in vitro* activity (<1% compared to undmodified rHuEPO; see Table 1). *In vitro* biological activity was measured by determining the incorporation of ^{59}Fe into cultured rat bone marrow cells after incubation with the modified EPO samples. As hematocrit is a measure of both the number of red blood cells and the size of red blood cells, and because red blood cells uptake iron, a decrease in iron incorporation by blood cells is indicative of a decrease in hematocrit, thus meeting a specific limitation recited in claim 35. Exposure of the chemically modified erythropoietin to the cells would be expected to result in their protection, maintenance or enhancement of viability. Thus, Satake anticipates claims 35-36.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 37-39 and 50-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brines et al. September 2000, *Proc Natl Acad Sci, USA*, 97(19): 10526-10531 (as listed on Applicant's IDS filed 9/2/04) in view of Satake et al. 1990, *Biochimica et Biophysica Acta*, 1038: 125-129 (as listed on Applicant's IDS filed 9/2/04), both in view of Ogden DA, 1989, *Seminars Nephrology*, 9(1): 12-15 (as listed on Applicant's IDS filed 9/2/04).

The claims are drawn to a method for the protection against or prevention of tissue injury or rejuvenation of tissue and tissue function in a mammal, comprising administering to the mammal a chemically modified erythropoietin that lacks at least one erythropoietic biological activity, wherein the injury is caused by inflammation (claim 38), wherein the chemically modified erythropoietin has at least one or more modified lysine residues or a modification of the N-terminal amino group (claim 39), wherein the erythropoietin can traverse an endothelial cell barrier (claim 50) such as the blood-brain barrier (claim 51), wherein the tissue comprises neuronal, capillary, or endothelial cells, among others (claim 52), wherein the tissue further comprises specific cell types (claim 53), and wherein said erythropoietin is a carbamylated erythropoietin having at least one carbamylated lysine residue or N-terminal amino group (claim 54).

Brines et al. teaches the administration of recombinant human erythropoietin (r-HuEPO) to rats that have been subjected to one of several brain insults, including focal ischemic stroke, blunt trauma injury to the brain, experimental autoimmune encephalomyelitis (EAE), and kainate-induced seizure. Each of these models will also inherently result in direct or indirect activation of inflammatory processes in the brain,

particularly within the EAE model, thus meeting a limitation of instant claim 38. Brines teaches that systemic administration of r-HuEPO was found to cross the blood-brain barrier (see p. 10528 and Fig. 1), thus meeting limitations of claims 50 and 51. Brines also teaches that pretreatment with r-HuEPO was significantly neuroprotective when in all of the above brain insult models. For example, in the rats subjected to focal ischemia, pretreatment with systemic r-HuEPO was found to significantly reduce infarct volume (see p. 10529, Fig. 3 for example), and in rats subjected to blunt trauma injury, the injury volume was significantly reduced in EPO-treated animals. Because of the considerable extent of the brain area rescued from tissue damage (better than 50% sparing of tissue damage in some instances, see Figs. 3 and 4 for example), the axons of ganglion cells (and therefore the viability of the ganglion cells themselves) would be expected to be included within the protected area, thus meeting limitations of claims 52 and 53. Finally, Brines concludes that r-HuEPO has the ability to protect brain tissue from a variety of insults including ischemia/hypoxia, as well as trauma, immune-mediated inflammation, and excessive neuronal excitation (see p. 10530, 2nd column). Brines, however, is silent with respect to chemically modified erythropoietin.

Satake et al. teaches the production of chemically modified r-HuEPO as discussed *supra*, and in particular a carbamylated r-HuEPO with modified lysine residues and lacking *in vitro* activity (see p. 126 1st column and Table 1). This chemically modified erythropoietin would thus meet limitations of instant claims 39 and 54.

Ogden teaches that patients treated with r-HuEPO (unmodified) sometimes report undesirable side effects, such as hypertension, which has even led in a few instances to seizures (p. 13, 1st column). Ogden suggests that the increased blood pressure observed in r-HuEPO-treated patients may be caused by a decrease in compensatory peripheral vasodilation (or conversely, an increase in vasoconstriction) without a commensurate decrease in the elevanted cardiac output (p. 13, 1st column). Ogden therefore suggests that patients undergoing therapy with r-HuEPO should be closely monitored for such adverse conditions.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of administering recombinant EPO to mammals to protect against tissue damage as taught by Brines et al. by chemically modifying the r-HuEPO, as taught by Satake et al. One of ordinary skill in the art would be motivated to do so because Ogden teaches that there are potential adverse effects associated with recombinant HuEPO therapy, such as hypertension potentially resulting from increased vasoconstriction and increased hematocrit. The chemically modified r-HuEPO taught by Satake et al. was shown to lack such erythropoietic effects *in vitro*, erythropoietic effects that would be unnecessary and undesirable in circumstances where tissue protection is the preferred EPO activity. The artisan would thus expect that administration of a chemically modified recombinant EPO could be successfully used to protect cells and tissues from tissue injury cause by inflammation because Brines demonstrates that r-HuEPO provides protection of neuronal tissues from inflammatory processes, and Satake shows that carbamylation of lysine resides on r-

HuEPO results in a loss of activity pertaining to erythropoietic activity. Taken together, such chemically modified (i.e. carbamylated) erythropoietin would be therapeutically valuable both for its tissue protective properties and also for its decreased capability to induce hypertension, which could potentially lead to other associated complications such as seizure or stroke.

Claims 37-39 and 50-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent 5,614,184 to Sytkowski et al., issued 25 March 1997 (as listed on Applicant's IDS filed 9/2/04) in view Satake et al. 1990, *Biochimica et Biophysica Acta*, 1038: 125-129 (as listed on Applicant's IDS filed 9/2/04), both in view of Ogden DA, 1989, *Seminars Nephrology*, 9(1): 12-15 (as listed on Applicant's IDS filed 9/2/04).

The claims are drawn to methods discussed *supra*. Sytkowski teaches modified erythropoietin proteins which have decreased biological activity relative to wild-type erythropoietin (see column 2, lines 56-61). These modified erythropoietins have a decreased ability to regulate growth and differentiation of red blood cell progenitor cells (see column 2 lines 61-64), thus meeting a specifically recited limitation within claim 37. Sytkowski also discloses that the modified erythropoietin proteins can be used for therapeutic purposes (see column 3, lines 48-50) and the administration of pharmaceutical compositions comprising these modified erythropoietins to individuals (see claims). The administration of erythropoietin, modified or unmodified, to an individual (i.e. a mammal) would be expected to inherently result in the protection

against or prevention of tissue injury or the restoration of tissue and tissue function following injury, such as injury caused by inflammation. Sytkowski discloses that erythropoietin proteins with decreased biological activity would be useful to decrease growth and differentiation of blood cell precursors in certain leukemias and polycythemias (see column 3, lines 53-57). Polycythemia vera is characterized by uncontrollable proliferation of red blood cells which can increase blood viscosity leading to hypertension and potentially stroke (see column 14, lines 29-34). Individuals receiving treatment for such conditions would also be in need of protection against the adverse effects inflammation caused either directly (i.e., leukemia) or indirectly (i.e., stroke) by the disorders. Sytkowski's silence as to the ability of erythropoietins to traverse an endothelial cell barrier does not negate the reality that traversing cell barriers is an inherent property of these proteins, a fact that was verified by subsequent researchers (see Brines et al., *supra*, for example). That the erythropoietin molecules can traverse endothelial cell barriers, such as the various cell barriers listed in claim 51, means that the molecules would further be inherently capable of contacting (i.e. protecting) each and every one of the recited tissues and cell types recited in instant claims 52 and 53. However, Sytkowski does not teach the specific chemical modifications recited in the claims such as modification of lysine residue(s) or N-terminal amino group, or carbamylated lysine residues.

Satake et al. teaches the production of chemically modified r-HuEPO as discussed *supra*, and in particular a carbamylated r-HuEPO with modified lysine residues and lacking *in vitro* biological activity, such as an increase in hematocrit (see p.

126 1st column and Table 1). This chemically modified erythropoietin would thus meet limitations of instant claims 39 and 54.

The teachings of Ogden are discussed *supra*.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of administering modified erythropoietin to individuals as taught by Sytkowski et al. in US Patent 5,614,184 by chemically modifying the erythropoietin as taught by Satake et al. One of ordinary skill in the art would be motivated to do so because Ogden teaches that there are potential adverse effects associated with recombinant HuEPO therapy, such as hypertension potentially resulting from increased vasoconstriction and increased hematocrit. The chemically modified r-HuEPO taught by Satake et al. was shown to lack such erythropoietic effects *in vitro*, erythropoietic effects that would be unnecessary and undesirable in circumstances where tissue protection is the preferred EPO activity. The artisan would thus expect that administration of a carbamylated EPO could be successfully used for therapy because Satake shows that carbamylation of lysine resides on r-HuEPO results in a loss of activity pertaining to erythropoietic activity, and Sytkowski teaches that such modified proteins with decreased biological activity (relative to wild-type proteins) are therapeutically useful.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kimberly Ballard, Ph.D.
Art Unit 1649
March 13, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER

UNITED STATES PATENT AND TRADEMARK OFFICE

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EXAMINER	
WANG, CHANG YU	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/351,640	BRINES ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-15,18-21 and 37-55* is/are pending in the application.

4a) Of the above claim(s) *6-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5,10-15,18-21 and 37-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/19/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/19/08 has been entered.

Status of Application/Amendments/claims

2. Applicant's amendment filed 6/19/08 is acknowledged. Claims 1, 16-17, and 22-36 are cancelled. Claims 2-5, 10-15, 20-21, 37, and 39 are amended. Claims 40-55 are newly added. Claims 2-15, 18-21, 37-39 and newly added claims 40-55 are pending in this application. Claims 6-9 are withdrawn without traverse (response filed 11/25/05) from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

3. Claims 2-5, 10-15, 18-21 and 37-55 are under examination in this office action.

4. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response.

5. Applicant's arguments filed on 6/19/08 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Objections

6. Applicant is advised that should independent claim 2 be found allowable, independent claim 21 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

7. In addition, claims 5 and 10 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 2 recites "protecting... isolated mammalian tissue, organ or body part....", which means the tissue, organ or body part has been isolated or removed from a mammalian body. Claims 5 and 10 are essentially identical to independent claim 2 because they recite the limitations "organ or tissue is isolated from a mammalian body" (claim 5) and "isolated by removing...from said mammalian body" (claim 10), which have been included in independent claim 2. Furthermore, claim 44 does not further limit claim 43 for the same reasons as set forth above.

8. Claims 18-20 are also objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Claims

18-20 depend from claims 7-9, which are non-elected claims. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

9. Applicant is advised that should claim 2 be found allowable, claims 5, 10 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In addition, should claim 43 be found allowable, claim 44 is a duplicate of claim 43.

Claim Rejections/Objections Withdrawn

10. The rejection of claims 2, 4, 5, 10, 12-15, and 19 under 35 U.S.C. 102(b) as being anticipated by Imai et al. (*Eur J Biochem*, 1990; 194:457-462) is withdrawn in response to Applicant's amendment by deleting "an isolated mammalian cell" and by reciting "during cold storage" to independent claim 2.

Claim Rejections/Objections Maintained

In view of the amendment filed on 6/19/08, the following rejections are maintained.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the

conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Applicant is advised that should claim 2 be found allowable, claims 5, 10 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In addition, should claim 43 be found allowable, claim 44 is a duplicate of claim 43 for the same reasons as set forth above.

Claims 2-5, 10-15, 18-21 and 37-55 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 6 of U.S. Patent No. 6,531,121 in view of Imai et al. (*Eur. J. Biochem.* 194: 457-462, as listed on applicant's IDS filed 4/24/03). Claims 2-5, 10-15, 18-21 and 37-55 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4 and 20-24 of copending Application No. 11/283,024. These rejections are maintained for the reasons made of record.

On p. 8 of the response, Applicant states that Applicant would file a terminal disclaimer once the claims are found to be allowable. With regard to the provisional

rejection, Applicant states that Applicant will not address the rejection since the rejection is provisional. Applicant's argument has been fully considered but it is not found persuasive.

The rejection of claims 2-5, 10-15, 18-21 and 37-55 under obviousness double patenting as being unpatentable over claims 1 and 6 of U.S. Patent No. 6,531,121 in view of Imai et al., and the rejection of the claims under obviousness double patenting as being unpatentable over claims 4 and 20-24 of copending Application No. 11/283,024 are maintained of record until a terminal disclaimer is filed. It is noted that traversal at the time of indication of allowable subject matter will not be considered timely.

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-5, 10-15, 18-21 and 37-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,824,672 (Simpkins et al., October 20, 1998) in view of Morishita et al. (*Neurosci.* 1997, 76(1): 105-116, as in IDS filed 4/24/03) and further in view of Imai et al. (*Eur. J. Biochem.* 1990, 194: 457-462, as IDS filed 4/24/03). The rejection is maintained for the reasons made of record.

On p. 10-11 of the response, Applicant argues no expectation of success at lower temperature and no expectation of success of using asialoEPO to protect tissues or organs. Applicant argues that neither Morishita nor Imai teaches EPO or asialoEPO would protect or maintain tissues, organs or body parts during cold storage. Applicant argues that Morishita teaches away from use of EPO to protect tissue at low temperature. Applicant further cites Somero (Annu. Rev. Physiol. 1995. 57:43-68) in support of the arguments. Applicant's arguments have been fully considered but they are not persuasive.

In contrast to Applicant's argument, the applied references do render the claimed method obvious because US5824672 (the '672 patent) teaches a method of preserving tissues during removal storage or organ transplantation, Morishita teaches use of EPO to protect neurons against glutamate toxicity (i.e. a result of ischemia or oxygen deprivation or hypoxia) and Imai teaches asialoEPO has the same activity of EPO for cell protection. Thus, it would have been obvious to replace EPO with asialoEPO for cell protection in the method of the '672 patent.

As previously made of record, although the protein expression or cellular signaling process would slow down at the lower temperatures or 4°C, neither Applicant nor the prior art shows that EPO or asialoEPO has lost its cell protection activity at the lower temperature or 4°C. Thus, EPO or asialoEPO would predictably have its cell protection activity at the lower temperature or at 4°C absent evidence to the contrary.

In addition, Applicant's interpretation with regard to the teaching of Morishita is incorrect. Morishita does not teach away from the claimed method because Morishita

teaches that only a short pre-exposure (5 min) to EPO is sufficient to provide protection to neurons against glutamate toxicity *in vitro* (see paragraph spanning pp. 111-112 of the Morishita reference). Furthermore, preservation of a body part or organ at 4°C is to slow down proteinase enzyme activity or to slow down metabolism of cells that would damage the tissue or to prevent the proliferation or infection of microorganisms in tissues or solutions. Thus, it is obvious to a skilled artisan at the time the invention was made to preserve the tissue in the presence of EPO or asialoEPO at the lower temperature. The skilled artisan would have been motivated to do so with an expectation of success because EPO and asialoEPO can protect cell survival and are expected to be effective at the lower temperature, and the viability of the tissues and organs can be maintained or enhanced at the lower temperature such as 4°C. Thus, the combined teachings of the '672 patent, Morishita and Imai are expected to be effective during cold storage as recited in amended claims, and thereby render the claimed method obvious.Note that

"The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)". See MPEP § 2144.07.

"Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. In re Kahn, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006)" See MPEP § 2143. 01-I.

Furthermore, new claims 40-55 are drawn to the same invention as original claims. Although independent claim 40 recites "organ or tissue from reperfusion injury", it is noted that the '672 patent also teaches such reperfusion injury. The '672 patent teaches a method of preserving tissues or organs during removal, storage and

implantation and also teaches that one source of injury that affects the success of tissue and organ transplantation is oxygen deprivation (i.e. hypoxia). This injury occurs when the regular flow of oxygenated blood to the tissue and cells is interrupted, such as during removal of an organ for transplantation (col. 1, lines 28-34) and reperfusion (col.2, lines 20-46; col.5, line 65-col.6, line 34). The limitations recited in the rest of dependent claims 41-55 are identical to dependent claims 10-15, 18-20 and 37-39, which have been addressed and rejected for reasons of record.

Conclusion

13. NO CLAIM IS ALLOWED.

14. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday from 8:30 AM to 6:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached at (571) 272-0911.

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/CYW/
Chang-Yu Wang, Ph.D.
September 9, 2008

/Christine J Saoud/
Primary Examiner, Art Unit 1647

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/351,640	01/24/2003	Michael Brines	10165-021	6828

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EXAMINER	
WANG, CHANG YU	
ART UNIT	**PAPER NUMBER**
1649	
MAIL DATE	**DELIVERY MODE**
03/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/351,640	BRINES ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-15 and 18-39* is/are pending in the application.

4a) Of the above claim(s) *6-9 and 24-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5, 10-15, 18-23 and 28-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application/Amendments/claims

1. Applicant's amendment filed 11/13/07 is acknowledged. Claims 1, 16-17 are cancelled. Claims 2, 21 are amended. Claims 37-39 are newly added. Claims 2-15, 18-36 and newly added claims 37-39 are pending in this application. Claims 6-9 and 24-27 are withdrawn without traverse (response filed 11/25/05) from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

2. Claims 2-5, 10-15, 18-23 and 28-39 are under examination in this office action.

3. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response.

4. Applicant's arguments filed on 11/15/07 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Maintained

In view of the amendment filed on 11/15/07, the following rejections are maintained.

Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226

(Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2-5, 10, 18-23, 28, 34, 35 and 37-39 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 6 of U.S. Patent No. 6,531,121 in view of Imai et al. (*Eur. J. Biochem.* 194: 457-462, as listed on applicant's IDS filed 4/24/03). The rejection is maintained for the reasons made of record in the office actions mailed 6/5/07, and as follows.

At p. 8 of the response, Applicant request that the rejection be held in abeyance until the allowable claims are indicated. Applicant's argument has been fully considered but it is not found persuasive.

The rejection of claims 2-5, 10, 18-23, 28, 34, 35 and new claims 37-39 under obviousness double patenting as being unpatentable over claims 1 and 6 of U.S. Patent No. 6,531,121 in view of Imai et al. is maintained of record as previously set forth with regard to claims 2-5, 10, 18-23, 28, 34, 35 until a terminal disclaimer is filed. It is noted that traversal at the time of indication of allowable subject matter will not be considered timely.

6. Claims 2, 4, 19, 21, 35 and new claims 37-39 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over

claims 4 and 20-24 of copending Application No. 11/283,024. The rejection is maintained for the reasons made of record in the office actions mailed 6/5/07 as applied to claims 2, 4, 19, 21, 35, and as follows.

At p. 8 of the response, Applicant states that Applicant will not address the rejection since the rejection is provisional. Applicant's argument has been fully considered but it is not found persuasive.

The rejection of claims under obviousness double patenting as being unpatentable over claims 4 and 20-24 of copending Application No. 11/283,024 is maintained of record until a terminal disclaimer is filed. It is noted that traversal at the time of indication of allowable subject matter will not be considered timely.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-5, 10-15, and 18-23 and 28-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,824,672 (Simpkins et al., October 20, 1998) in view of Morishita et al. (*Neurosci.* 1997, 76(1): 105-116, as listed on applicant's IDS filed 4/24/03) and further in view of Imai et al. (*Eur. J. Biochem.* 1990, 194: 457-462, as listed on applicant's IDS filed 4/24/03). The rejection is maintained for the reasons made of record in the office actions mailed 6/5/07, and as follows.

At p. 10-11 of the response, Applicant argues that it would not be expected to use EPO in preserving tissues or organs to be effective because the timing taught by Morishita is not suitable for maintaining the cell, tissue or organs during surgery or transplantation. Applicant argues that Morishita teaches that a minimum of 8 hours is required for the neuroprotective effect of EPO and Imai teaches study on the proliferation-stimulating activity of asialoEPO over several days. Applicant's arguments have been fully considered but they are not persuasive.

In contrast to Applicant's argument, as previously made of record and as duly quoted by Applicant on p. 11 of the response, Morishita teaches that only a short pre-exposure (5 min) to EPO is sufficient to provide protection to neurons against glutamate toxicity *in vitro* (see paragraph spanning pp. 111-112 of the Morishita reference). Thus, the claimed method is expected to be effective based on the teaching of Morishita and thereby the applied references render the claimed method obvious. Note that

"The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)". See MPEP § 2144.07.

"Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. In re Kahn, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006)" See MPEP § 2143. 01-I.

At p. 12 of the response, Applicant argues that a skilled artisan would not have expected that EPO-mediated tissue protection would be effective at low temperatures because neither Morishita nor Imai teaches that EPO would be active at lower temperatures. Applicant's arguments have been fully considered but they are not persuasive.

In response, although the protein expression or cellular signaling process would slow down at the lower temperatures or 4°C, Applicant fails to demonstrate that the EPO or asialoEPO would have lost its activity of cell protection at the lower temperature absent evidence to the contrary. In addition, it is noted that only claim 38 recites 4°C. It is known in the art that preservation of a body part or organ at 4°C is to slow down proteinase enzyme activity or to slow down metabolism of cells that would damage the tissue or to prevent the proliferation or infection of microorganisms in tissues or solutions. Thus, it is obvious to a skilled artisan at the time the invention was made to preserve the tissue in the presence of EPO or asialoEPO at the lower temperature. The skilled artisan would have been motivated with an expectation of success based on what is known in the art about preservation at a low temperature to maintain the viability of the tissues and organs at the lower temperature such as 4°C as recited in claim 38. Note that

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955)

At p. 12-13 of the response, Applicant argues that non-neuronal tissues were not expected to be protected by EPO or asialoEPO because none of the cited references teach the protection of non-neuronal tissues as recited in new claim 39. Applicant argues that Imai teaches promoting formation of erythroid colonies in vitro and Morishita teaches neuroptrotective activity of EPO in vitro. Applicant's arguments have been fully considered but they are not persuasive.

In contrast, the applied references provide an expectation of success in non-neuronal tissue protection. Although Imai does not explicitly teach non-neuronal tissue protection by EPO or asialoEPO, Imai teaches detection of an increase of activity of asialoEPO or EPO in ^{59}Fe-incorporation assay and increased colony forming activity using mouse bone marrow cells (i.e. non-neuronal cells) (p. 460, 1st col. and Table 2 & p. 460, 1st col. and Figure 4). The increased activity of asialoEPO or EPO in Fe-incorporation and colony forming activity in cultured bone marrow cells indicate that asialoEPO or EPO can promote proliferation and survival of bone marrow cells (i.e. non-neuronal cells), which is an activity of non-neuronal protection. Thus, a skilled artisan would have an expectation of success in use of asialoEPO or EPO for non-neuronal protection of isolated cells, tissues or organs during transplantation or surgery by combing the teachings of the '672 patent with the teachings of Morishita and Imai. Accordingly, it would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of enhancing cell viability in organs removed for transplanting taught by the '672 patent by administering EPO to these organs to protect against hypoxia, as taught by Morishita et al. and improve the efficiency of protection activity of EPO by use of asialoEPO as taught by Imai et al. because Imai teaches that asialoEPO has improved characteristics in vitro and more effective than EPO.

"The selection of a known material based on its suitability for its intended use supported a prima facie obviousness determination in *Sinclair & Carroll Co. v. Interchemical Corp.*, 325 U.S. 327, 65 USPQ 297 (1945)". See MPEP § 2144.07.

"Obviousness can be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so. In re Kahn, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006)" See MPEP § 2143. 01-I.

Further, it would be routine practice to optimize the particular dosages or temperatures or time as recited in instant claims 20 and 36-38, to determine the optimal amount to administer, and the skilled artisan would be motivated to do so based upon "[t]he normal desire of scientists or artisans to improve upon what is already generally known", see MPEP 2144.05. Thus, absent some demonstration of unexpected results from the claimed administration amounts, this optimization would have been obvious at the time of applicant's invention. Note that

In the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a *prima facie*case of obviousness exists. *In re Wertheim*, 541 F.2d 257, 191 USPQ 90 (CCPA 1976); *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990), See MPEP 2144.05-I

"[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456, 105USPQ 233, 235 (CCPA 1955)" See MPEP 2144.05-II

As previously made of record, Imai et al. teach an asialoEPO dose range applied to the cells of 0.1 to 1600 pg/ml, which is administered in an amount substantially overlapping with the claimed range as recited in instant claims 20 and 36 (i.e. about 1 μg to about 12 mg per kg of cell). Finally, the '672 teaches different tissues, organ or body part including muscle, heart, lung, liver, kidney, small intestine, capillary endothelial, testes, ovary and endometrial as recited in instant claim 39 (see col. 3, lines 30-65). Accordingly, the combined teachings of the above references render obvious the instant invention of claims 2-5, 10-15, 18-23 and 28-39.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2, 4, 5, 10, 12-15, and 19 stand rejected under 35 U.S.C. 102(b) as being anticipated by Imai et al. (*Eur J Biochem*, 1990; 194:457-462). The rejection is maintained for the reasons made of record in the office actions mailed 6/5/07, and as follows.

At p. 13-14 of the response, Applicant argues that Imai et al. do not teach all the claim limitations because Imai only demonstrates the proliferation-stimulating activity of asialoEPO on cells in cell culture. Applicant also argues that Imai does not teach the claimed method because Imai's method is conducted at 37°C for days. Applicant's arguments have been fully considered but they are not persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., temperature and time) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In this case, the instant claims 2, 4, 5, 10, 12-15, and 19 fail to recite 37°C and time as stated by Applicant. As previously made of record, Imai et al. teach administration of human asialoerythropoietin (asialoEPO) to various isolated mouse

cells, such as bone marrow cells. (see p. 461, figure 4), which meet the limitations as recited in instant claim 2 because Imai teaches that addition of asialoerythropoietin to mouse bone marrow cells (i.e.erythropoietin-responsive cells) *in vitro* enhances the colony-forming activity (i.e. a measure of the viability and/or function) of the cells. The colony-forming activity involves differentiation and proliferation of the cells, which are a measure of the viability and/or function of the cells and which would thus meet the instantly recited limitation of "maintaining the viability or function of an isolated mammalian cell" of claim 2. In addition, the cells exposed to asialoEPO were isolated from the mouse body and were cultured in medium comprising the asialoEPO, wherein culturing in medium is akin to perfusing and/or bathing the cells *ex vivo* (i.e., an artificial environment outside the body) as recited in instant claims 4, 5, 10-15 and 19. Accordingly, the teachings of Imai et al. anticipate instant claims 2, 4, 5, 10, 12-15, and 19.

Conclusion

9. NO CLAIM IS ALLOWED.

10. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

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/CYW/
Chang-Yu Wang, Ph.D.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/351,640	01/24/2003	Michael Brines	10165-021	6828

7590 06/05/2007

Frederick Hamble
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EXAMINER
BALLARD, KIMBERLY A

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
06/05/2007	PAPER

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The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/351,640	BRINES ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

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- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-15 and 18-36* is/are pending in the application.

4a) Of the above claim(s) *6-9 and 24-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5,10-15,18-23 and 28-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 28, 2007 has been entered.

The request for the Revocation and Power of Attorney submitted in the response filed February 28, 2007 has been noted and entered of record.

Claim 20 has been amended and new claims 21-36 have been added as requested in the response filed February 28, 2007. Following the amendment, claims 2-15 and 18-36 are pending in the current application

Claims 6-9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 25, 2005. Newly added claims 24-27 also read upon the nonelected species and are similarly withdrawn from further consideration.

Accordingly, claims **2-5, 10-15, 18-23** and **28-36** are under examination in the instant office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Claim Objections

The objection to claim 20 set forth at pages 2-3 of the previous office action (08/28/2006) is withdrawn in view of Applicant's amendment to the claim.

Maintained Claim Rejections

Obviousness-Type Double Patenting

The rejection of claims 2-5, 10, 18 and 19 on the ground of nonstatutory obviousness-type double patenting over claims 1 and 6 of US Patent No. 6,531,121 in view of Imai et al. is maintained for reasons of record set forth at p. 7 in the office action mailed December 13, 2005. Further, newly added claims 20-23, 28, 34 and 35 are similarly rejected for reasons of record in said office action. The Examiner notes that Applicant intends to file a terminal disclaimer upon an indication of allowable subject matter. However, until a terminal disclaimer is received, the rejection of said claims is maintained.

Claim Rejections - 35 USC § 103

The rejection of claims 2-5, 10-15 and 18-20 under 35 USC 103 as being unpatentable over US Patent 5,824,672 (Simpkins) in view of Morishita et al. (*Neurosci*, 1997; 76(1):105-116) and Imai et al. (*Eur J. Biochem*, 1990; 194:457-462) is maintained for reasons of record. Additionally, newly added claims 21-23 and 28-36 are similarly rejected for reasons of record.

In the response filed February 28, 2007, Applicants argue that the cited references do not teach or suggest hat administering asialoEPO cold protect or maintain the viability or function of an isolated mammalian cell, tissue, organ or body part, since none of the cited references teaches or suggests that asialoerythropoietin has tissue-protective properties. For examples, Applicants assert that the Examiner has incorrectly characterized the subject matter of the Imai reference, because Imai teaches that the "biological activity" of asialoerythropoietin refers to erythrocyte production and not tissue protection, which protective property is independent of erythropoietic activity. Applicants also assert that the Morishita reference does not teach or suggest exposure to EPO during or after cytotoxic injury would protect the cultured cells, and further that an 8-hour preincubation period is essential for the manifestation of EPO's protective effect. Moreover, Applicants quote Morishita as stating (p. 114, 2nd column) that EPO may not "meet the requirement for neuroprotection in submaximal but severe hypoxia or ischemia, both which cause degeneration of neurons vulnerable to these insults," and therefore argue that the skilled artisan would not have had a reasonable expectation of success that EPO would be protective under *ex vivo* conditions where the cell, tissue,

organ, or body part is disconnected from the natural blood circulation. Applicants additionally argue that because asialoerythropoietin is inactive *in vivo*, and Morishita teaches that pre-incubation is essential, the skilled artisan would be led away from administering asialoerythropoietin prior to the isolation of the cell or tissue, etc. Finally, Applicants assert that there is no basis for equating the *in vitro* activity in Imai with the *ex vivo* activity of the present invention, and thus the cited references provide no reasonable expectation of success.

Applicants' arguments have been fully considered but they are not persuasive. In response to applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

As Applicants duly note, Morishita teaches that only a short pre-exposure (5 min) to erythropoietin is sufficient to provide protection to neurons against glutamate toxicity *in vitro* (see paragraph spanning pp. 111-112 of the Morishita reference). The skilled artisan, thinking in terms of isolation of cells, tissues, organs or body parts for the eventual purpose of transplantation of the tissue, would look at such information favorably, because there may not be time to provide for a lengthy pre-exposure period once a resolution is made to remove a tissue or organ for transplantation. The fact that asialoerythropoietin has a shortened half-life *in vivo* is therefore inconsequential, because only a brief exposure to asialoerythropoietin would be necessary in order to confer protective effects. Once removed, the *ex vivo* cell, tissue, organ, etc. would

receive the full benefits of asialoerythropoietin because metabolization of the protein is no longer a factor *in vitro*. Additionally, Applicants appear to have misconstrued the teachings of Morishita (as noted above), wherein EPO may not "meet the requirement for neuroprotection in submaximal but severe hypoxia or ischemia, both which cause degeneration of neurons vulnerable to these insults." In this section (p. 114, 2nd column), Morishita discusses EPO that is endogenously produced in the CNS in response to hypoxic injury. Such conditionally expressed, *endogenous* EPO is what Morishita discusses as being insufficient to provide neuroprotection in severe cases of ischemia or hypoxia; Morishita is not referring to *exogenously administered* EPO in this case.

Moreover, contrary to Applicants' allegation that the teachings of Imai would not lead the skilled artisan to use asialoerythropoietin in an *ex vivo* method, the skilled artisan would recognize that if one biological activity of a cytokine is enhanced, it is reasonable to expect that all of its biological activities would be enhanced, thus including protective effects of the cytokine. Imai explicitly states that "these results demonstrate that asialoerythropoietin binds to its receptor faster than the intact (EPO) form" (see Abstract, p. 457). One of skill in the art would therefore recognize that a molecule having a faster binding velocity would undoubtedly result in higher biological function for *all* of its activities. Therefore, the skilled artisan would have a reasonable expectation that exposing an isolated cell, tissue, organ or body part to asialoerythropoietin either *in vivo* for a short period or *ex vivo* (which is synonymous with *in vitro* – see, for example, definition of "*ex vivo*" downloaded from Dictionary.com

on 05/15/2007) for a more extensive period would be capable of protecting the cell, tissue, etc. from hypoxic injury. Further, it would be routine practice to optimize the particular dosages, as recited in amended claim 20 and new claim 36, to determine the optimal amount to administer, and the skilled artisan would be motivated to do so based upon "[t]he normal desire of scientists or artisans to improve upon what is already generally known", see MPEP 2144.05. Thus, absent some demonstration of unexpected results from the claimed administration amounts, this optimization would have been obvious at the time of applicant's invention. Accordingly, the combined teachings of the above references render obvious the instant invention of claims 2-5, 10-15, 18-23 and 28-36.

New Claim Rejections

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2, 4, 19, 21 and 35 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 4 and 20-24 of copending Application No. 11/283,024. Although the conflicting claims are not identical, they are not patentably distinct from each other because the '024 application contains claims directed to a method for protecting or maintaining the viability of a responsive mammalian cell, tissue or organ from injury comprising administering a pharmaceutical composition comprised of an erythropoietin or a tissue protective cytokine, wherein the erythropoietin is chemically modified and is human asialoerythropoietin, which would render obvious the instantly claimed method of protecting or maintaining the viability or function of an isolated mammalian cell, tissue, organ or body part. Claim 4 of the '024 application also recites that asialoerythropoietin is administered prior to, within or after the therapeutic window recognized for the currently approved therapeutic for the injury, which would address limitations of instant claim 4, reciting administration prior to, during, or after isolation of the cell or tissue, which the skilled artisan would recognize as causing tissue injury. Accordingly, the claims of the '024 application render obvious instant claims 2, 4, 19, 21 and 35.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2, 4, 5, 10, 12-15, 19 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Imai et al. (*Eur J Biochem*, 1990; 194:457-462).

The claims are drawn to a method for protecting or maintaining the viability or function of an isolated mammalian cell, tissue, organ or body part comprising an erythropoietin-responsive cell or tissue, said method comprising administering to a mammalian cell, tissue, organ or body part an amount of asialoerythropoietin for a duration effective to protect said viability or function. Further claimed limitations include: wherein said administration is prior to, during, or after isolation (claim 4), wherein the cell, tissue, organ or body part is isolated from a mammalian body (claim 5) by removing it from said mammalian body (claim 10), wherein said administration is by the perfusion *in situ* or *ex vivo* (claim 12), wherein the administration is ex vivo and the asialoerythropoietin is proved in a perfusate solution (claim 13) or a preservation solution (claim 14), wherein the administration is by continuous perfusion, pulsatile perfusion, infusion, bathing, injection, or catheterization (claim 15), wherein the asialoerythropoietin is human asialoerythropoietin (claim 19), and wherein the amount of asialoerythropoietin administered is between about 100 ng to about 50 mg per kg of the cell, tissue, organ or body part (claim 20).

Imai et al. teach the administration of human asialoerythropoietin to various isolated mouse cells, such as bone marrow cells. For example, Figure 4 (p. 461) demonstrates that addition of asialoerythropoietin to mouse bone marrow cells *in vitro*, which are erythropoietin-responsive cells, enhances the colony-forming activity of the cells. The colony-forming activity involves differentiation and proliferation of the cells, which are a measure of the viability and/or function of the cells and which would thus meet the instantly recited limitation of "maintaining the viability or function of an isolated mammalian cell" of claim 2. In this instance, the cells were exposed to asialoerythropoietin after isolation from the mouse body (see Figure 4 legend). The cells were cultured in medium comprising the asialoerythropoietin, wherein culturing in medium is akin to perfusing and/or bathing the cells *ex vivo* (i.e., an artificial environment outside the body), which the skilled artisan would recognize is the same as saying "*in vitro* culturing of cells or tissue". Finally, Imai et al. teach an asialoerythropoietin dose range applied to the cells of 0.1 to 1600 pg/ml. If the average wet weight of a cell is about 1300 pg (see, for example, bioinformaticsservices.com/bis/resources/cybertext/chapter3.html, first posted on December 3, 1998), and in this instance Imai was using 10^5 cells/ml, then amount of asialoerythropoietin administered to the cells would be in the range of about 1 μg to about 12 mg per kg of cell, which substantially overlaps with the claimed range. Accordingly, the teachings of Imai et al. anticipate instant claims 2, 4, 5, 10, 12-15, 19 and 20.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on Monday-Friday 9AM - 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elizabeth C. Kemmerer

Kimberly Ballard, Ph.D.
May 15, 2007

ELIZABETH C. KEMMERER. PH.D.
PRIMARY EXAMINER

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/351,640	01/24/2003	Michael Brines	10165-021	6828

7590 08/28/2006

Frederick Hamble
712 Kitchawan Road
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EXAMINER	
BALLARD, KIMBERLY A	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 08/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/351,640	BRINES ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-15 and 18-20* is/are pending in the application.

4a) Of the above claim(s) *6-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5,10-15 and 18-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

Applicant's response, declaration, and amendments filed 13 June 2006 is acknowledged. Claims 3, 18 and 19 have been amended. Claims 2-15 and 18-20 are currently pending, wherein claims 6-9 have been withdrawn as being drawn to a nonelected species. Accordingly, claims **2-5**, **10-15** and **18-20** are under examination in the instant office action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Upon further consideration, the species election for erythropoietin-responsive species put forth in the 01 September 2005 office action at page 2, paragraph 3 is hereby *withdrawn*. The species of isolated mammalian cells, tissues, organs or body parts are rejoined.

Claim Objections

Claim 20 is objected to because of the following informalities: the claim recites the phrase "asialoerythropoietin per kg body weight" in line 3 which had been deleted in the previous version of the claims (11/25/2005). The inserted phrase is not underlined

nor does the claim status indicate that the claim is "currently amended." Applicant's attention is directed to 37 CFR 1.121(c) (see MPEP 714), which states:

> All claims being currently amended in an amendment paper shall be presented in the claim listing, indicate a status of "currently amended, " and be submitted with markings to indicate the changes that have been made relative to the immediate prior version of the claims. The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived.

Because, however, the status of the claim recites "Previously Amended", the Examiner assumes that the phrase has been reinserted through typographical error. Appropriate correction is required.

Withdrawn Objections or Claim Rejections

The objection to the specification set forth at page 3 of the previous office action (12/13/2005) is hereby withdrawn in view of Applicant's amendment to the specification.

The objection to claims 18 and 19, as set forth at page 3 of the previous office action (12/13/2005), is hereby withdrawn in view of Applicant's amendments to the claims.

The rejection of claims 2-5, 10-15, 18 and 20 under 35 U.S.C. 112, first paragraph, as set forth at pp. 3-6 of the previous office action (12/13/2005) is hereby

withdrawn in view of Applicant's arguments and declaration by the inventor Dr. Michael Brines (Exhibit B). The specification would reasonably allow a person skilled in the art to practice the method on other isolated cells, tissues, organs or body parts.

Maintained Rejections

Obviousness-Type Double Patenting

The rejection of claims 2-5, 10 and 18 on the ground of nonstatutory obviousness-type double patenting over claims 1 and 6 of US Patent No. 6,531,121 in view of Imai et al. is maintained for reasons of record set forth at p. 7 in the previous office action (12/13/005). Further, amended claim 19 is similarly rejected for reasons of record in said office action. The Examiner notes that Applicant intends to file a terminal disclaimer upon an indication of allowable subject matter. However, until a terminal disclaimer is received, the rejection of said claims is maintained.

Claim Rejections - 35 USC § 103

The rejection of claims 2-5, 10-15, 18 and 20 under 35 USC 103 as being unpatentable over US Patent 5,824,672 (Simpkins) in view of Morishita et al. and Imai et al. is maintained for reasons of record. Additionally, amended claim 19 is now included in said rejection for reasons of record and reasons discussed below.

In the response filed 13 June 2006, Applicant's argue that Simpkins does not disclose the use of erythropoietin (EPO) to address hypoxia associated with transplantation, Morishita does not suggest the use of EPO to address hypoxia resulting

from *ex vivo* storage of an organ and only teaches EPO administration prior to insult, and Imai only evaluates erythropoietic effects, not tissue protective activities, of asialoEPO *in vitro*. Applicant thus argues that that combination of Simpkins, Morishita and Imai would not render the current invention obvious.

Applicant's arguments have been fully considered but they are not persuasive.

In response to applicant's argument that the combination of references would not render the current invention obvious, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references to justify combining their teachings. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

For example, the skilled artisan would recognize the need for improving the viability of cells, tissues, and organs that are injured by oxygen deprivation when they are removed from a donor and maintained outside of the body prior to implantation into a recipient, as addressed by Simpkins at column 1, lines 28-34 and column 2, lines 12-17. The skilled artisan would also recognize that it would be beneficial to apply a tissue protective compound prior to, during, and after excision of the tissue from the donor to minimize damage caused by hypoxia associated with transplantation of the cell, organ or tissue, also as addressed by Simpkins at column 4, lines 16-33. Morishita teaches a means for protecting against hypoxia using EPO. That Morishita et al. applied EPO prior to injury in their studies is irrelevant not only because the timing of administration is

already addressed by the teachings of Simpkins as discussed above, but also because as Applicant duly notes, Morishita determined that a short exposure to EPO was sufficient to exert protective effects, thus suggesting the potency of EPO is such that extensive pre-incubation with EPO prior to tissue insult is not necessary. Finally, the skilled artisan would recognize that the improved *in vitro* characteristics of asialoerythropoietin (asialoEPO) taught by Imai, such as greatly enhanced affinity for the EPO receptor and enhanced *in vitro* biological activity, would be beneficial under *ex vivo* conditions. Imai additionally teaches the use of recombinant human erythropoietin in the production of asialoEPO (see p. 457 under Asialoerythropoietin), thus meeting the recited limitation of amended claim 19. The skilled artisan would therefore reasonably expect that asialoEPO would be more effective than EPO in exerting tissue protective effects *in vitro* or *ex vivo* based on the combined teachings of Imai and Morishita. Taken together, the combined references would render obvious the instant invention of claims 2-5, 10-15, and 18-20.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Kimberly Ballard, Ph.D.
Art Unit 1649
August 22, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/351,640	01/24/2003	Michael Brincs	10165-021	6828

7590 12/13/2005

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Ossining, NY 10562

EXAMINER	
BALLARD, KIMBERLY A	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 12/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/351,640	BRINES ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

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- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-15 and 18-20* is/are pending in the application.

4a) Of the above claim(s) *6-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5,10-15,18 and 20* is/are rejected.

7)☒ Claim(s) *19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/24/03, 9/2/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The Amendment, Remarks, and Revocation and Power of Attorney filed November 25, 2005 are acknowledged. The Applicant has canceled claims 16-17. Claims 2-15 and 18-20 are pending and under examination in this office action.

Election/Restrictions

Applicant's election without traverse of the species (c) organs, as the erythropoietin responsive species; (g) after isolation, as the timing of administration of asialoerythropoietin in relation to isolation of the cell, tissue, organ, or body part; (k) removing said cell, tissue, organ, or body part, as the method of isolation; and (m) ex vivo, as the administration of asialoerythropoietin by perfusion, in the reply filed on November 25, 2005 is acknowledged. Claims 6-9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species of methods of isolating the cell, tissue, organ, or body part, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 25, 2005.

Information Disclosure Statement

Signed and initialed copies of the IDS forms submitted April 24, 2003 and September 2, 2004 are enclosed in this action.

Specification

The use of the registered trademark CELSIOR has been noted in this application (e.g., p. 29). It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

Claim 18 is objected to because of the following informalities: claim 18 recites dependency upon canceled claims 16-17. Appropriate correction is required.

Claim 19 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot stem from another multiple dependent claim, in this case claim 18. See MPEP § 608.01(n). Accordingly, the claim has not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-5, 10-15,18 and 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for maintaining the viability or function of isolated neuronal cells, does not reasonably provide enablement for a method for maintaining the viability or function of other isolated cells, tissues, organs or body parts. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are drawn to a method for protecting or maintaining the viability or function of an isolated mammalian cell, tissue, organ or body part comprising an erythropoietin-responsive cell or tissue, said method comprising administering to a mammalian organ an amount of asialoerythropoietin for a duration effective to protect said viability or function, wherein the Applicant has elected the species of an organ. The claims are further drawn to protection from damage resulting from hypoxic conditions, administration of asialoerythropoietin after isolation of the organ, isolation of the organ for transplantation, administration of asialoerythropoietin *ex vivo* in a preservation solution by continuous perfusion, pulsatile perfusion, infusion, bathing, injection or catheterization, wherein the mammal is a human, and wherein the amount of asialoerythropoietin administered is between about 50 to about 350 ng/ml.

It is well-known in the art that erythropoietin (EPO) is responsible for the regulation of red blood cell production, and that EPO production is stimulated by reduced oxygen content in the renal arterial circulation (Faruki and Kiss, Transfusion Medicine Update, The Institute for Transfusion Medicine, July 1995). An unexpected

finding by the applicant and others (see Brines et al., 2000, *PNAS*, 97: 10526-10531 and Morishita et al., 1997, *Neurosci.* 76(1): 105-116, both listed on applicant's IDS filed 4/24/03) revealed that EPO also has a neuroprotective effect in the case of brain injury *in vivo* and in glutamate-induced neuronal death *in vitro*. However, the instant specification provides only one working example of asialoerythropoietin being administered for the purpose of protecting or maintaining viability of an isolated mammalian structure, the administration being *in vitro* to cultured P19 cells, a neural-like embryonal carcinoma cell line.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

Because of the complex nature of the invention, the artisan would require further guidance for other cell types and for isolated organs in particular to be able to use the invention as intended with an expectation of success. The prior art further does not provide compensatory teachings as to the use of erythropoietin or asialoerythropoietin for the maintenance of tissues or organs other than for negating the negative effects associated with brain damage or ischemia in neuronal tissues. Therefore, knowledge of the use of erythropoietin in neuroprotection does not provide predictability about its

ability to provide similar protective or maintenance effects on other tissues, in particular isolated whole organs removed from the body.

For these reasons, which include the complexity and unpredictability of the nature of the invention, the lack of teachings in the prior art, the lack of direction and guidance for treating removed tissues or organs, the one limited working example of in vitro protection of neuronal-like cells, and the breadth of the claims for types of organs the invention would encompass, it would require undue experimentation to use the invention commensurate in scope with the claims.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2-5, 10 and 18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 6 of U.S. Patent No. 6,531,121 in view of Imai et al. (*Eur. J. Biochem.* 194: 457-462, as listed on applicant's IDS filed 4/24/03). The claims are drawn to a method for protecting or maintaining the viability or function of an isolated human cell, tissue, organ or body part comprising administering asialoerythropoietin. Because the administration of asialoerythropoietin is to an isolated cell, tissue or organ, then it would follow that the organs would be subjected to hypoxic conditions (claim 3), that the organs would be isolated from a mammalian body (claim 5) by removal (claim 10), and that the administration of asialoerythropoietin is after isolation of the organ (claim 4).

The '121 patent recites a method for protecting or maintaining the viability of a cell, tissue or organ in a human or mammal, comprising administering asialoerythropoietin. The patent claims are drawn to methods of administering asialoerythropoietin *in vivo*, whereas the instant application claims are drawn to methods of administering asialoerythropoietin *ex vivo* or *in vitro*. Imai et al. report that both the specific activity and the receptor binding velocity of asialoerythropoietin are many times higher than that of erythropoietin *in vitro* than *in vivo*, presumably because asialoerythropoietin is metabolized much more rapidly *in vivo* than is erythropoietin. It would have therefore been obvious to the person of ordinary skill in the art at the time the invention was made to modify the '121 patent reciting a method for protecting tissues, cells and organs by administering asialoerythropoietin *in vivo* to a method for protecting or maintaining the viability of these isolated components *in vitro*. The person

of ordinary skill in the art would have been motivated to administer asialoerythropoietin *ex vivo* instead of *in vivo* in this method with a reasonable expectation of success because it was demonstrated by Imai et al. that asialoerythropoietin was much more active *in vitro* than *in vivo*, so isolated organs, tissues or cells administered asialoerythropoietin *in vitro* (*ex vivo*) would benefit more than those tissues or organs administered asialoerythropoietin *in vivo*.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2-5, 10-15, and 18 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,824,672 (Simpkins et al., October 20, 1998) in view of Morishita et al. (*Neurosci.* 1997, 76(1): 105-116, as listed on applicant's IDS filed 4/24/03) and in further view of Imai et al. (*Eur. J. Biochem.* 1990, 194: 457-462, as listed on applicant's IDS filed 4/24/03).

The claims are drawn to a method for protecting or maintaining the viability or function of an isolated mammalian organ comprising an erythropoietin-responsive cell or tissue, said method comprising administering to a mammalian organ an amount of asialoerythropoietin for a duration effective to protect said viability or function. The claims are further drawn to protection from damage resulting from hypoxic conditions,

administration of asialoerythropoietin after isolation of the organ, isolation of the organ for transplantation, administration of asialoerythropoietin *ex vivo* in a preservation solution by continuous perfusion, pulsatile perfusion, infusion, bathing, injection or catheterization, wherein the mammal is a human, and wherein the amount of asialoerythropoietin administered is between about 50 to about 350 ng/ml.

U.S. Patent 5,824,672 discloses a method for preserving tissues during removal storage and implantation by enhancing cell viability in a population of graft cells during the transplantation procedure (abstract). Graft cells are defined as those cells, tissues or organs obtained from a donor for transplantation into a recipient wherein the graft cells may be derived from human subjects or from animals (column 3, lines 31-34). Graft cells are treated with an effective dose of a polycyclic phenolic compound, conferring cytoprotection on the cells (column 2, lines 20-28). The '672 patent also discloses that the methods of the invention may be applied to any or all of the procedures involving perfusing the tissue at a time that is during excision from the donor, perfusing or immersing or otherwise exposing the tissue during storage (i.e. *ex vivo*), and treating the tissue after transplantation into the recipient (column 4, lines 16-22). Further, the '672 patent teaches that graft cells treated *ex vivo* with polycylic phenolic compounds exhibited increased viability compared to untreated cells (column 6, Example 3).

US Patent 5,824,672 discloses that one source of injury that affects the success of tissue and organ transplantation is oxygen deprivation (i.e. hypoxia). This injury occurs when the regular flow of oxygenated blood to the tissue and cells is interrupted,

such as during removal of an organ for transplantation (column 1, lines 28-34). However, the '672 patent does not teach the use of asialoerythropoietin for the protection or maintenance of isolated organs for transplantation.

Morishita et al. teach the use of erythropoietin in the protection of neuronal cells from glutamate-induced neurotoxicity *in vitro*. The amount of erythropoietin used in this study is reported as 3-300 pM (approximately 0.1 to 10 ng/ml). Morishita reports that erythropoietin prevented glutamate-induced cell death in a dose-dependent manner in neurons cultured with erythropoietin for 24 hours prior to exposure to glutamate (p. 107, 2nd column). Exposure of neurons to glutamate in culture simulates what occurs during ischemic or hypoxic injury, as Morishita notes that a massive increase in the extracellular concentration of glutamate is thought to be responsible for the neuronal death caused by reduction in oxygen (p. 106, 1st column). In other words, Morishita teach the use of erythropoietin in protecting or maintaining the viability of cultured cells under hypoxia conditions. Morishita does not, however, teach the use of asialoerythropoietin for this process.

Imai et al. teach that while asialoerythropoietin, which is desialylated erythropoietin, has approximately the same activity as intact erythropoietin *in vivo*, asialoerythropoietin showed a 3-4-fold greater *in vitro* activity that the intact form in a ^{59}Fe-incorporation assay using mouse bone marrow cells (p. 460, 1st column and Table 2). Additionally, the colony-forming activity of asialoerythropoietin on mouse bone marrow cells was found to be approximately 6-fold higher than the intact form of erythropoietin (p. 460, 1st column and Figure 4). Moreover, a time course experiment

demonstrated that asialoerythropoietin binds to the erythropoietin receptor 5 times faster than intact erythropoietin.

It would have been obvious to the person of ordinary skill in the art at the time the invention was made to modify the method of enhancing cell viability in organs removed for transplanting taught by the '672 patent by administering erythropoietin to these organs to protect against hypoxia, as taught by Morishita et al. One of ordinary skill in the art would be motivated to do so because the '672 patent teaches a need for improving cell viability and teaches that hypoxia is a factor in the loss of such viability, and Morishita teaches a means for protecting against hypoxia. The artisan would thus expect that erythropoietin could be successfully used to protect viability as instantly claimed, since it protects against hypoxia. It would further be obvious to use asialoerythropoietin as taught by Imai et al. instead of the erythropoietin taught by Morishita, because Imai teaches that asialoerythropoietin has improved characteristics in vitro. Thus, the artisan would expect it to be more effective than erythropoietin.

Conclusion

No claims are allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on M-F 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Kimberly Ballard, PhD
Art Unit 1649
December 8, 2005

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/573,905	05/30/2006	Michael Brines	WP03-1 A04-US 10165-042-999	2092

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ART UNIT	PAPER NUMBER
1647	

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11/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,905	BRINES ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,37-45 and 47-69* is/are pending in the application.

4a) Of the above claim(s) *1,37,38,40,49-55,57-66,68 and 69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39,41-45,47,48,56 and 67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/29/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment, filed 13 November 2007, has been entered in full. Claim 1 was amended. Claims 2-36 were canceled. New claims 37-69 were entered.

Applicant's election with traverse of Group III (claims 39, 41-45, 47, 48, 56, 67) and species election of a chemically modified EPO having one or more modified lysine residues or a modification of the N-terminal amino group (i.e. claim 42 vii) and species election of mutated species S100E in the reply filed on 04 August 2008 is acknowledged. The traversal is on the grounds that Group IX (claim 68) determines whether a chemically modified or mutated EPO treats, prevents, delays the onset of, or reduces complications associated with adhesions by (1) inducing sepsis, adhesions or inflammation in a mammal; (2) administering the chemically modified or mutated EPO to the mammal; and (3) determining the adhesion score in the mammal to determine if less adhesions resulted from the administration of the chemically modified or mutated EPO. Applicant maintains that examining both Groups together would not impose an undue burden on the Examiner.

Applicant's arguments have been fully considered but are not found persuasive. Group III is drawn to a method of treating/preventing/delaying the onset of/reducing adhesion formation, abnormal fibrous band formation and formation of a connection between organs or scarring comprising administering an EPO to a subject. Group IX (claims 68 and 69) is drawn to a method for testing the ability of a modified EPO to treat/prevent/delay the onset of/reduce ***not only adhesion formation, but sepsis and***

inflammation from infection, wherein sepsis, adhesion or a combination thereof **is induced in the mammal, comprising administering a modified EPO to said mammal**, then determining an adhesion score. Group III and Group IX are directed to methods that recite functionally distinct steps. In addition, the methods are drawn to treating different patient populations, which may or may not overlap. A search to identify documents relevant to the patentability of the claimed methods would not necessarily employ the same or similar search terms and techniques to identify relevant documents. As such, it would be burdensome to search the inventions of the Groups together. The requirement is still deemed proper and is therefore made FINAL.

Claims 1, 37, 38, 40, 49-55, 57-66, 68 and 69 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group, there being no allowable generic or linking claim. Election was made **with** traverse in the reply filed on 10 September 2007. Claims 39, 41-45, 47, 48, 56 and 67 are under examination. The claims will only be examined to the degree that they reflect the elected invention.

Information Disclosure Statement

The information disclosure statement(s) (IDS) filed (29 July 2008) was received and complies with the provisions of 37 CFR §§1.97 and 1.98. There are 26 pages of references (A01-C402). They have been placed in the application file and the information referred to therein has been considered as to the merits. It noted that the IDS list various Office Actions and a patent interference. These references have been

considered by the Examiner, but will not be printed on the face of the patent issuing from this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39, 41-45, 47, 48, 56 and 67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method of **treating, delaying the onset of, or reducing** adhesion formation, abnormal fibrous band formation, formation of a connection between organs or scarring in a mammal, comprising administering to the mammal a therapeutically effective amount of **an erythropoietin (EPO) that is chemically modified at lysine residues or the N-terminal amino group, wherein said chemical modification is carbamylation at lysine residues or the N-terminal amino group** and a pharmaceutical acceptable carrier.

does not reasonably provide enablement for:

a method of **preventing** adhesion formation, abnormal fibrous band formation, formation of a connection between organs or scarring in a mammal, comprising administering to the mammal a therapeutically effective amount of **an unmodified EPO** (i.e. "**at least one erythropoietin (EPO) that is optionally** chemically modified or

mutated"; the Examiner understand "*optionally* chemically modified or mutated" to encompass EPOs that are unmodified**) or an EPO with any type of chemical modification or an EPO with any type of mutation** and a pharmaceutical acceptable carrier.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification teaches that carbamylated EPO does not retain erythropoietic activity and fails to bind with the classic homodimer EPO receptors, but advantageously maintains the tissue protective functionality of endogenous EPO (page 12, line 32-page 13, line 5). The specification teaches carbamylation of EPO via chemical modifications of the amino terminus or side chain of lysine (pages 13-14). The specification teaches variant EPOs wherein one or more sites in EPO have been mutated (page 14). The specification teaches S100E wherein the amino acid at position 100 has been changed to a glutamic acid (page 14, lines 15-16). The specification teaches the use of a rat abdominal sepsis model, wherein the animals are monitored for formation of adhesions (pages 29-30). A cumulative adhesion score is calculated for each animal 24 hours post-injury. Animals receiving carbamylated EPO had fewer adhesions than animals receiving saline (page 32 and page 34). The specification also teaches that animals receiving carbamylated EPO had a much higher survival rate and less scarring than animals receiving recombinant erythropoietin (rhEPO)(page 35).

The instant claims are not supported by an enabling disclosure for the following reasons:

The specification fails to teach the prevention of adhesion formation, abnormal fibrous band formation, formation of a connection between organs or scarring in a mammal upon EPO administration. Prevent means to completely stop a condition from occurring. "Prevention" is not a relative term, it is total. A very high degree of evidence is required, which is accepted in the art, that an absolute protection from the pathology exists over an extended period of time.

The specification fails to demonstrate that EPO with ***any type of chemical modification*** can treat, delay the onset of, or reduce adhesion formation, abnormal fibrous band formation, formation of a connection between organs or scarring in a mammal. Satake et al. (reference of record; Biochimica et Biophysica Acta, 1038:125-129, 1990) teach that modification of the positive charges of the lysine residues to neutral or negative charges, such as in acetylation, trinitrophenylation, carbamylation or succinylation cause a significant loss of recombinant human erythropoietin activity. ***However,*** guanidination of amino groups of the lysine residues yielded derivatives that showed **higher biological activities** *in vitro* than native recombinant human EPO. Amidination of lysine residues had no effect on the activity. **The novelty of the instant is that the EPO does not retain erythropoietic activity (thus avoiding the risk of high hematocrit levels, thrombosis) but still has the tissue protective activity.** The art teaches that modifications in the EPO sequence are critical to the protein's

structure/function relationship. These modifications can either increase or decrease erythropoietic activity.

Furthermore, the specification fails to demonstrate that EPO with ***any type of EPO mutation (including those mutations EPO point mutations recited in claims 43-45)*** can treat, delay the onset of, or reduce adhesion formation, abnormal fibrous band formation, formation of a connection between organs or scarring in a mammal. The specification teaches variant EPOs wherein one or more sites in EPO have been mutated (page 14). The specification fails to teach the use of any of the recited mutant EPOs in a rat abdominal sepsis model, wherein the animals are monitored for the formation of adhesions and cumulative adhesion scores are calculated. Yasuda et al. (US 7,300,916 B2) *teach the treatment of scars using EPO antagonists* (abstract, column 1, lines 1-16; column 3, lines 1-36; column 6, line 60-column 7, line 36 and claims). Yasuda et al. teach that EPO receptor proteins and anti-EPO antibodies bind to EPO to block binding of EPO to an EPO receptor. Thus, the Yasuda data teaches the use of EPO antagonist for scar treatment versus the instant application which teaches the use of EPO for scar treatment. An EPO with any type of mutation (including those mutations EPO point mutations recited in claims 43-45) could act as antagonists and/or have the opposite effect of the claimed activity. The mutant EPOs could retain erythropoietic activity and bind the classic homodimer EPO receptors. Conceivably, the mutant EPOs could fail to bind the classic homodimer EPO receptors, but still lack the biological activity of treating, delaying the onset of, or reducing adhesion formation, abnormal fibrous band formation, formation of a connection between organs or scarring

in a mammal. It is known for proteins that even a single amino acid change/mutation can destroy or affect the function of the biomolecule. The effects of these changes are largely unpredictable as to which ones have a significant effect versus not. It would require an indeterminate quantity of fundamentally unpredictable investigational experimentation of the skilled artisan to determine whether any mutant modifications of EPO, as encompassed by the claims, could be used in an *in vivo* manner (i.e. treating adhesion formation, scarring, etc) in a mammal, wherein said EPO lacks or is diminished of erythropoietic activity (i.e. increase in hemoglobin concentration, hematocrit or thrombosis).

Lastly, the instant claims recite the limitation, **"..at least one** erythropoietin (EPO) that **is optionally** chemically modified or mutated..". This limitation encompasses EPOs that are unmodified. The specification fails to demonstrate that unmodified EPO can treat, delay the onset of, or reduce adhesion formation, abnormal fibrous band formation, formation of a connection between organs or scarring in a mammal. Example 3 from the instant specification clearly demonstrates that animals receiving carbamylated EPO had a much higher survival rate and less scarring than animals receiving recombinant erythropoietin (rhEPO; i.e. unmodified).

Due to the large quantity of experimentation necessary to show that the onset of the claimed condition has been prevented; the large quantity of experimentation necessary to make an EPO with any type of chemical modification or any type of mutation; the large quantity of experimentation necessary to demonstrate that an EPO with any type of chemical modification or any type of mutation can be employed an *in*

vivo manner (for treating adhesion formation, scarring, etc) in a mammal, wherein said EPO lacks or is diminished of erythropoietic activity; the lack of direction/guidance presented in the specification regarding same; the absence of working examples; the complex nature of the invention; the contradictory state of the prior art which teaches that EPO antagonists can be used to treat scars (see Yasuda et al.), the unpredictability of the effects of chemical modifications on EPO function (see Sataka et al.), and the breadth of the claims which fail to recite limitations regarding chemical modifications and mutations in EPO, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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11/17/08